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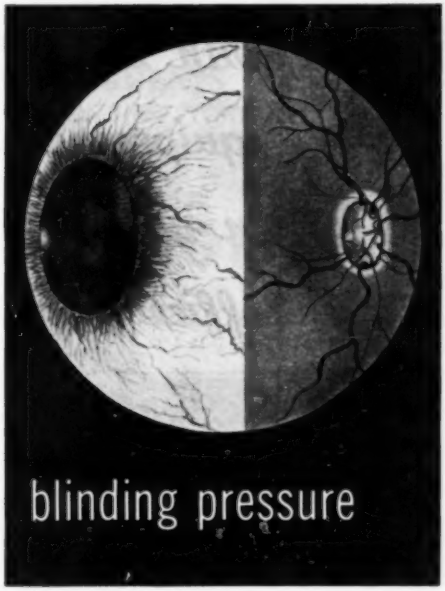

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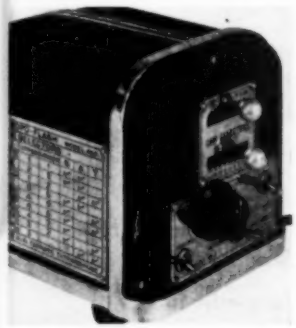

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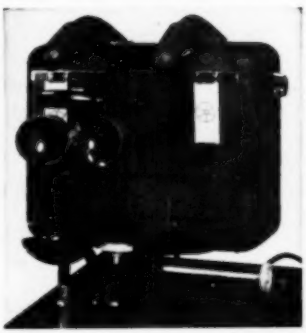

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AMERICAN JOURNAL OF OPHTHALMOLOGY

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RETROLENTAL FIBROPLASIA IN PREMATURE INFANTS*

II. STUDIES ON THE PROPHYLAXIS OF THE DISEASE: THE USE OF ALPHA TOCOPHERYL ACETATE

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A new concept of retrolental fibroplasia was introduced by our previously reported observations on the early stages and development of the disease.[1] These observations demonstrated that retrolental fibroplasia starts in the retina with an acute onset in postnatal life and runs an active course, which gradually subsides. The final picture depends upon the severity of the acute phase and the extent of contracture of the fibrous tissue formed during the active stage of the disease.

Retrolental fibroplasia was first brought to attention by Terry,[2] who described the appearance of the fully developed disease and pointed out the relationship of the disease to prematurity. Reese and Payne,[3] Krause,[4] and Klien[5] made further reports on cases they had observed in the late stages of the disease.

In the earlier literature there was considerable difference of opinion as to the nature and origin of the membrane behind the lens. Various hypotheses had been proposed relating the disease to the persistence and overgrowth of the hyaloid artery or primary vitreous, or to a generalized maldevelopment of both the cerebral and ocular neuroectoderm occurring during the early stages of fetal life. In addition the question of whether or not the disease was present at birth remained unsettled.

The main reason for these differences in opinion arose from the fact that the earlier reports had been limited almost entirely to clinical and pathologic examinations made when the disease was well advanced. None of the earlier observers had seen where the disease started, when it first began, or how it progressed. It therefore seemed logical that the first step in the investigation of the pathogenesis should be the observation of the onset and course of the disease. To do this, it was necessary to make observations on prematurely born children shortly after birth and to continue the observations periodically until the disease had reached the end stages described by the previous investigators.

The observations made on this plan showed that retrolental fibroplasia was not present at birth. No differences were found on early examinations between the eyes that subsequently developed retrolental fibroplasia and those that did not. The earliest detectable change, occurring about 3 to 5 weeks after birth, was a dilatation of the retinal veins and an increased tortuosity of the retinal arteries. Localized or generalized swelling of the retina soon followed, and the retina developed a grayish-green color. Often the retina became so swollen that the course of the retinal vessels could not be traced in the areas of greatest retinal edema. The vitreous became cloudy and proliferating fibrous bands extended forward from the elevated retina into the vitreous. The retrolental membrane was formed by the

* From the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital and University. Presented in part at the eighth clinical meeting of the Wilmer Residents Association, April, 1949.

fusion of the vitreous bands and the peripheral folds of swollen elevated retina. These findings have been confirmed by Falls,[6] Unsworth,[7] and Gilger.[8]

The active phase of the disease usually stops between the 4th and 5th month of the infant's life, and the changes that occur after this time are due to contracture of previously formed fibrous tissue. If the membrane behind the lens is complete, all vision is lost. Occasionally the disease is not so extensive and, when it subsides, only a partial membrane or a band resembling a retinal fold is formed. These eyes are often myopic and may show disseminated areas of irregular pigmentation. Some vision is retained and children with this less severe involvement see well enough to walk alone and play with toys. In premature infants both eyes are affected by the disease, but often to various degrees. The membrane may be complete in one eye and only partial in the other.

The main problem in retrolental fibroplasia is the prophylaxis of the disease rather than treatment in the late stages when irreversible damage has been done to the retina. No treatment has yet been found which is of value when the disease is well established. Operations to remove the membrane have been unsuccessful, for a portion of the retina itself is excised in the attempt to clear the retrolental space. The description of the onset and course of retrolental fibroplasia has redirected most of the thinking about the disease. Formerly, emphasis was placed on factors which might have been effective in the prenatal life of the infants[9] or to an abnormal persistence of various fetal structures. It is now evident that the most fruitful investigation is to be found in a study of factors which are active in postnatal life.

Etiologic Considerations

In our first report the idea was proposed that the disease might be related to a metabolic disturbance produced by some of the newer methods used in the care of premature infants to compensate for their physiologic immaturity. The close correlation between the incidence of retrolental fibroplasia and the birth weight of the infant adds support to the theory that a metabolic abnormality may be the cause of the disease.

One of the main physiologic differences between the premature and the full-term infant is the defective fat metabolism of the premature infant.[10] Because of this defect, premature infants have been given diets low in fat and high in protein as they apparently can utilize protein efficiently.[11]

Shortly after the high protein diets were introduced it was found that a disturbance was created in the metabolism of the aromatic amino acids. Phenylalanine and tyrosine were found to be incompletely oxidized and the intermediary products p-hydroxyphenyl pyruvic and p-hydroxyphenyl lactic acid appeared in the urine. This abnormal metabolism of aromatic amino acids could be prevented by increasing the amount of vitamin C in the diet.[12] It seemed possible that some similar metabolic disturbance might be the basis for the occurrence of retrolental fibroplasia.

The low fat diet recommended for premature infants contains very little of the fat-soluble vitamins. In view of this fact and the poor absorption of fats by the premature infant, a minimal supply of fat-soluble vitamins would be available to the premature infant were they not supplemented. It seems probable that the premature infant might have a marginal prenatal storage of a necessary fat-soluble substance. As this substance is depleted or the need for it increased in postnatal life, the infant might be unable to replenish it from the diet. This hypothesis can be correlated with the clinical observation that the earliest detectable changes of retrolental fibroplasia are noted about one month after birth. Of the fat-soluble vitamins, A, D, K, and E, the vitamins A and D have been provided routinely in large doses in the vitamin supplements currently used. Vitamin K is usually given shortly after birth. Vitamin E alone of the fat-soluble vitamins has not routinely been in-

cluded in the vitamin supplements of premature infants. It is known that regardless of how high the maternal intake of vitamin E may be, the newborn rat begins life with a negligible supply of this vitamin.[13]

In addition to the low vitamin E available in the reduced fat diets, and the poor absorption of fat-soluble substances by the premature infant, the amount of vitamin E available might be further reduced by two factors in the current care of premature infants. The first factor is the use of large amounts of vitamin A given to supplement the diet. The vitamin-A supplements are given usually either in the form of natural fish-liver oils which contain large quantities of unsaturated fats, or as vitamin A in water-miscible preparations. It has been shown that the requirement of vitamin E in experimental animals is increased when vitamin A[14] or when unsaturated fats[15] are administered. This is thought to be due to the role of vitamin E as an antioxidant in protecting the unsaturated carbon bonds in these compounds.[16] Therefore the supplements of large amounts of vitamin A, or of fish-liver oils containing unsaturated fats, might serve to increase the needs for vitamin E in the diet of the premature infant. The use of iron to overcome the anemia which premature infants develop in postnatal life might serve to decrease even further any small amount of vitamin E available to the premature infant. It is well known that ferric salts destroy vitamin E. One of the methods of producing a vitamin-E deficient diet for experimental animals is to treat the ingredients of a full diet with ferric chloride to destroy the vitamin E present.[17]

Kinsey and Zacharias found a positive correlation between the rise in incidence of retrolental fibroplasia and the increased use of water-miscible preparations of vitamins and of iron.[18] The relationship of large supplements of vitamin A and iron to the occurrence of retrolental fibroplasia is still under study. In the premature nursery of The Johns Hopkins Hospital retrolental fibroplasia developed in two infants who had not received vitamin A or iron. Two other children have been seen here with retrolental fibroplasia in the late stages of the disease who had also never received either vitamin A or iron supplements. Kinsey and Zacharias have reported similar cases, and it is likely, as they point out, that the administration of large amounts of vitamin A and iron are not primary factors in the etiology of the disease.

From these considerations, it is apparent that numerous factors in their dietary regime would allow premature infants to have only marginal amounts of vitamin E available. Among these factors are the low fat diet, the poor absorption of fats by the premature infants, the lack of vitamin-E supplements, and the use of such substances as vitamin A, unsaturated fats, and iron, all of which might increase the need for vitamin E.

In addition, the relative importance of fat metabolism in the immediate neonatal period, plus the predominant absorption of unsaturated fatty acids by the premature infant might further increase the vitamin-E requirements in this critical period.[10] Soon after birth, newborn infants have a sudden increase in the metabolism of lipoid substances. The fetus probably uses little fat for its heat production but stores considerable for later emergencies. After the newborn infant has fairly well depleted its glycogen stores, it begins to depend largely upon reserves of fat for energy. There is a greatly increased transport of fat substances in the blood so that the concentration of most types of blood fat are roughly doubled between birth and the second week of life.[19] Recent studies on the biochemical function of vitamin E indicate that many of its physiologic effects are related to its antioxidant properties, especially in relation to fat metabolism. Vitamin E functioning as an antioxidant plays an important role in protecting or stabilizing unsaturated fats during their mobilization, metabolism, and storage within tissue cells.[20]

The immature organism is particularly

susceptible to vitamin-E deficiency. Nursing rats born of vitamin-E depleted mothers develop acute muscular dystrophy 17 to 19 days after birth.[21] Young chickens, placed on a vitamin-E deficient diet at the time of hatching, suddenly develop nutritional encephalomalacia at 3 to 4 weeks of age.[22] This disease is characterized by areas of edema, hemorrhage, necrosis, and glial proliferation in the central nervous system. In each of these diseases, there is an age limit to the susceptibility of the animals to the nutritional derangement. As they grow older the incidence of the disease steadily decreases.[23] This susceptibility of immature animals to vitamin-E deficiency might be paralleled by the susceptibility of premature infants to retrolental fibroplasia.

A further function of vitamin E is to control excessive tissue oxidation. The lowering of the oxygen consumption of brain homogenates of vitamin-E deficient animals by alpha tocopheryl phosphate appears to be due to the prevention of the reduction of cytochrome-C wherever the cytochrome system comes into play; whether in carbohydrate, fat, or protein metabolism.[24] Since the retina has a higher rate of respiration than that of almost any other tissue,[25] and since the premature infant is characteristically in a marginal status of anoxia[19] vitamin-E supplements might be expected to play a role in the prevention of retrolental fibroplasia through this function.

These considerations immediately raised the question whether supplements of vitamin E might prove to be a factor in the prevention of retrolental fibroplasia. In an effort to study the problem of retrolental fibroplasia from this standpoint, a series of laboratory and clinical investigations have been undertaken. These investigations are still in progress, and this report covers only the observations on the clinical aspects. The results of the laboratory studies will be reported in another paper.

Clinical Study

The clinical study on the use of dl alpha tocopheryl acetate was begun in June, 1948. At that time the only available preparation suitable for premature infants was a mixture of natural tocopherols of low potency. Vitamin-E activity is possessed by three higher alcohols known as alpha, beta, and gamma tocopherol. Alpha tocopherol has the greatest biologic activity of these three forms. Tocopherols are widely distributed in vegetable oils and in lesser concentration in animal fats. Their esters are much more stable than the free forms.[26] Synthetic dl alpha tocopheryl acetate has been accepted as the international standard of vitamin E.[27] In July, 1948, a special preparation of synthetic dl alpha tocopheryl acetate in a water-miscible menstrum was obtained.*

For a period of 10 months, alternate infants admitted to the premature nursery of The Johns Hopkins Hospital with birth weights of three pounds (1,360 gm.) or less were given supplements of this preparation. The dose used was 150 mg. daily, given orally in 50 mg. doses every eight hours between feedings. This was started as soon after birth as the infant was able to take feedings by gavage or by mouth. Most of the infants in each group received 9,000 units of vitamin A and 900 units of vitamin D daily in a water-miscible preparation. About one third of the infants in each group received 4 cc. of a 10-percent solution of ferric ammonium citrate daily. This iron supplement was begun when the infants were six weeks of age.

During this 10-month period, 11 infants received vitamin-E supplements and none developed retrolental fibroplasia. Fifteen infants in the control group did not receive vitamin E, and five of these developed retrolental fibroplasia.

These results were so encouraging that in May, 1949, the plan was changed and vitamin-E supplements were given to all premature infants weighing three pounds (1,360 gm.) or less at birth. The routine ad-

* We are indebted to Hoffmann-La Roche, Inc., Nutley, New Jersey, for the dl alpha tocopheryl acetate used in this study.

ministration of vitamin A and iron was discontinued. Each infant was given 500 units of vitamin D daily in a water-miscible preparation. Since this time 12 infants have received alpha tocopherol supplements.

One of them has developed retrolental fibroplasia, showing massive retinal folds extending from the disc to the periphery of the fundus in each eye. The neonatal course of this infant was unusual. The birth weight of the infant was 1,110 gm. This fell to 880 gm. by the second week of life. The infant was apneic and cyanotic, and not expected to survive. Because of its poor condition, the only nourishment it received for 11 days after birth was parenteral glucose and amigen. From the 11th to the 15th day, feedings by gavage could be given, but only glucose solution was tolerated. On the 15th day, milk feedings could be substituted for the glucose solution. It was necessary to continue feedings by gavage until the infant was six weeks of age. The alpha tocopherol could not be started until the 11th day when feedings by gavage were begun.

Before the time alpha tocopheryl acetate was used, a total of 63 infants weighing less than three pounds at birth were followed routinely. Of these, 12 developed retrolental fibroplasia.

In summary the experience with the entire group of infants followed routinely from birth can be divided into three periods: (1) The period before the use of alpha tocopheryl acetate supplements, (2) the period during which alternate infants were given alpha tocopheryl acetate supplements, and (3) the period during which all infants were given the supplements. All of these infants had a birth weight of three pounds (1,360 gm.) or less. A total of 101 infants was observed. Seventy-eight of these did not receive alpha tocopheryl acetate supplements. Seventeen of these (21.8 percent) developed retrolental fibroplasia. In contrast, 23 infants received alpha tocopheryl acetate supplements. Only one of these (4.4 percent) developed retrolental fibroplasia (table 1).

As mentioned before, during the period when alternate infants with birth weights of 1,360 gm. (three pounds) or less were given tocopherol supplements, five infants in the unsupplemented group developed the early stages of retrolental fibroplasia. In addition four infants in the group weighing over 1,360 grams who did not receive vitamin E prophylactically showed the early stages of the disease. The preparation of dl alpha tocopheryl acetate was used in these nine babies to determine whether vitamin-E supplements would alter the course of the disease in its early stages. Vitamin A and iron preparations were withheld from these infants when the vitamin-E supplements were begun. Under this regime, progress of the lesions was arrested in five cases. In the other four cases, the course of the disease was unaffected by the supplement. Spontaneous regression of the disease after the stage of diffuse retinal exudation is unusual.

In our experience thus far, vitamin-E supplements are of no value if not started at least before the baby is six weeks of age, since by that time irreversible retinal changes have occurred. The supplement must be started early before the retina has become detached and visible as a partial or complete membrane behind the lens. It is of no value when the disease is recognized grossly by the parents or doctor by external examination.

No serum levels of vitamin E in prema-

TABLE 1

EFFECT OF VITAMIN E SUPPLEMENTS ON THE INCIDENCE OF RETROLENTAL FIBROPLASIA IN PREMATURE INFANTS WITH BIRTH WEIGHTS OF THREE POUNDS (1,360 GM.) OR LESS

Diet	Number of Infants	Number with Retrolental Fibroplasia	Percent Retrolental Fibroplasia
Supplemented with Vitamin E	23	1	4.4
Not Supplemented with Vitamin E	78	17	21.8

ture infants have been reported in the literature. The normal level in adults has been found to vary from 1.0 to 1.2 mg. percent.[30] Only a few determinations have been reported on full-term newborn infants. These levels were significantly lower than the maternal levels, and varied from 0.2 to 0.5 mg. percent.[31, 32]

Determinations of the vitamin-E levels of the serum have been made in the course of this study. At first the determinations were made by a method[28] which required 5 cc. of blood—an amount which was not feasible to obtain frequently from small premature infants. It became evident that a micromethod for determining vitamin E was essential. Dr. V. E. Kinsey solved this problem for us by adapting a method devised by M. L. Quaife which requires only 0.2 cc. of serum.[29] The vitamin-E determinations on the sera are being made at present under Dr. Kinsey's direction at the Harvard Medical School. Forty-six determinations of the vitamin-E level were made on sera of premature infants who were receiving no vitamin-E supplements. The average level in these determinations was 0.25 mg. percent. When dl alpha tocopheryl acetate was given, the serum level rose with increasing supplements. The average vitamin-E level was 4.12 mg. percent in 103 determinations made on sera of infants receiving 150 mg. dl alpha tocopheryl acetate daily. Most of these infants had birth weights of three pounds or less, and the sera were obtained from 2 to 8 weeks after birth.

It is important to follow the serum level of tocopherol for, in a few of our cases, the serum tocopherol level did not rise even though the infants were receiving large oral supplements of dl alpha tocopheryl acetate. The problem of parenteral administration of alpha tocopherol to premature infants who show evidence of inadequate absorption by the oral route is now being investigated.

Comment

In evaluating our experience with tocopherol supplements, there are several observations for which an explanation is not readily available. There appears to be no constant correlation between the serum tocopherol level and the occurrence of retrolental fibroplasia. Some of the infants in the unsupplemented group who developed retrolental fibroplasia did not have lower tocopherol levels than some infants in the same group who did not develop the disease. In addition the one infant in the supplemented group who developed retrolental fibroplasia showed progression of the disease even though the serum tocopherol level was adequate from the time the first retinal changes were observed at six weeks of life. As stated before the exact mechanism whereby vitamin E functions in the body is not known. It seems apparent, however, that at the high serum tocopherol levels we have obtained, the tocopherol is not exerting a true vitamin function but rather a pharmacologic action as suggested by Harris.[33]

The material presented in this paper is the report of studies still in progress. It must be remembered that, as yet, no claims for the role of vitamin E in human nutrition have been substantiated, although its role in animal nutrition has been well established. So far the results in the prophylaxis of retrolental fibroplasia have been encouraging, and it is planned to continue these studies until sufficient data have been accumulated to evaluate critically the role of vitamin E in relation to this disease. It seems certain that the solution to the etiology of retrolental fibroplasia will be found from such a metabolic study.

Conclusions

1. A total of 101 premature infants with birth weights of 1,360 gm. (three pounds) or less have been observed at routine intervals since birth. Twenty-three of these infants received supplements of dl alpha tocopheryl acetate. One of these (4.4 percent) developed retrolental fibroplasia. Seventy-eight infants did not receive supplements of dl alpha tocopheryl acetate. Seventeen of these (21.8 percent) developed retrolental fibroplasia.

2. The average serum tocopherol level in the unsupplemented group of premature infants was 0.25 mg. percent. On a dosage of 50 mg. of dl alpha tocopheryl acetate every eight hours, the average serum tocopherol level rose to 4.12 mg. percent.

The Johns Hopkins Hospital (5).

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THE PHYSIOLOGY OF THE INTRAOCULAR FLUIDS AND ITS CLINICAL SIGNIFICANCE*

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I find it impossible to proceed with this lecture without a preface recording my great appreciation of the fact that this academy has made me its guest of honor. I know that on an occasion such as this it is the usual and graceful habit of the lecturer to express such thanks; but in this case I would wish you to believe that my thanks are more than usually sincere and from the heart. Before the war on more than one occasion I was a guest in this great country and drank deep of American hospitality. During the war one of the good things—and there are some good things even in war—was the close association which I and my British colleagues had with Americans, particularly American ophthalmologists. After the war one of the sorrows of peace was the departure of our American friends from England; but I, for my part, having grown used to your company, have made up for my loss by recurrent invasions of your country. In 1946, I was made the guest of honor of the select company of the American Ophthalmological Society and also of the Association for Research; in 1947, I was again the guest of honor of the wider company of the ophthalmologic section of the American Medical Association; and today I am overwhelmed by a similar courtesy from what must certainly be the largest convention of ophthalmologists in this world. I have to thank you, Mr. President, and your council —and you all—for thus filling my cup to overflowing; and I hope you will believe me when I assure you that to come and be with you is to me not to come amongst strangers to a foreign land, but to meet again very old and very dear friends—to go, as it were, from one room to another in my own home through a door which is never locked.

Some of you may remember that about a quarter of a century ago I summarized my early work on the problem of the mechanism of the formation of the intraocular fluids in a monograph wherein I stated, unequivocally and with all the assurance of youth, that the aqueous humor was a dialysate of the capillary blood. Fortunately I had the wisdom, even in those days, to end the monograph thus: "This is to be accepted in the light of a working hypothesis which may, or may not, aid after the manner of a temporary scaffolding in the erection of a building of whose very design we are ignorant, and as such it is to be treated. For the whole progress of knowledge is strewn with the wrecks of such systems." However much or little the formulation of this hypothesis stimulated work on this problem, the fact remains that today such a theory can no longer stand alone: it is to explore what must take its place and what practical lessons must follow that is the purpose of this address.

This necessity to discard a hypothesis, of course, is not at all uncommon in the advance of any science and is essentially a sign of progress. The methods of investigation available 25 years ago were crude in comparison with those of today: they produced results with a large margin of error which could be synthesized into broad and apparently satisfying generalizations. But today the introduction and evolution of improved and novel techniques have changed all this. The accuracy of chemical analyses, particularly of minute quantities of fluids, has improved enormously; but what is of much greater importance, to the chemistry of molecules there has been added the physics

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of radioactive tracer elements whereby we can follow metabolic processes throughout all their intricacies without, so far as we know, upsetting the normal metabolism. By these electronic techniques it is relatively easy to determine the rate of penetration of a given element from the blood stream into the uvea, the aqueous humor, the vitreous, the lens, or the cornea in quantities so minute as to be quite outside the range of chemical analysis. With this technique we have gained immeasurably in refinement of accuracy, ease in manipulation, and—a very important point—in lack of disturbance of the natural conditions.

It is not surprising that with these new weapons at our disposal, with all their refinement of accuracy, we are getting results differing from the old and we have been confronted with many new awkward facts which will not fit in with a picture so simple as that of a dialysate. It follows that the conception of a dialysate must be abandoned and something else must take its place. It frequently occurs, however, that in the evolution of science from a relatively simple to a more complex stage, the transference is a period of considerable confusion and complexity. To a large extent we are at present in the confusion of this interim period, and so, if I choose this opportunity to put forward a new theory, I would hasten to deprive it of any proved or pragmatic significance. If it merely serves as another temporary scaffolding whereon to build and eventually has to be discarded on the discovery of further new facts, it may have served its purpose of ordering our present knowledge and stimulating new avenues for research.

I like to think it is often valuable and frequently stimulating not to make our science too rigid and pontifical, but to anticipate that which is wholly verifiable. Those who refuse to go beyond fact rarely get as far as fact; they will miss much of the fun of life. Goethe may have been right when he said that hypotheses are cradle songs which lull to sleep; but if one sleeps one may dream dreams, and perhaps awake to write a sonnet. And if for a few days I have escaped from the factual fetters of nationalized medicine in Britain into a community where medicine is still—if perhaps only temporarily—free, I hope to make the most of my liberty and take you along with me on a journey in the hope that, even if we do not reach the end with certainty, we may find some illumination by the way. In any event the journeying is always more pleasant than reaching the goal.

Here then are some facts.

I do not think there is any doubt but that the essential blood-aqueous barrier is the capillary walls, as in fact they are the blood-tissue barrier elsewhere in the body. It is true that in the ciliary region the further barrier of the ciliary epithelium is interposed, which, as we shall see presently, exerts a considerable influence on the composition of the intraocular fluid; but on the anterior surface of the iris there is no other barrier, for there the capillaries are naked to the aqueous, and posteriorly the tenuous internal limiting membrane of the retina can have little physiologic significance. A multitude of experiments on the transfer of materials both naturally occurring and artificially injected, both in the normal state and in conditions of increased capillary permeability, as well as clinical facts such as the possibility of the maintenance of a relatively normal physiology when the eye is divided into compartments by a seclusion of the pupil, leave little doubt that an exchange between blood and intraocular fluid throughout the vascularized tissues of the eye constitutes the background of the metabolic interchange.

With this premise I want to examine for a moment the transfer of material across the walls of the ocular capillaries. Table 1 indicates the rate of transfer both into the aqueous humor and into the vitreous body of certain substances. These substances are chosen from many on which we have ex-

perimented as being typical examples of classes, and for comparative purposes their respective rates are expressed in terms of a constant which has a relative but no absolute significance.

TABLE 1

RATE OF TRANSFER: BLOOD→EYE

Substance (and molecular weight)		Aqueous K_{Aq}	Vitreous Kv
Water	(18)	600	—
Lipoid Soluble Substances:			
Ethyl alcohol	(46)	250	150
Sulfapyridine	(249)	100	30
Thiourea	(76)	70	—
Sugars:			
Glucose	(180)	34	11
Sucrose	(342)	5	0.29
Inulin	(5000)	nil	nil
Ions:			
Sodium	(23)	40	7.5
Chloride	(35)	40	6
Thiocyanate	(58)	46	7.5
Nitrogenous Substances:			
Urea	(60)	14	1
Amino acids	(75)	14	0.3
Penicillin	(334)	1.3	nil
Proteins: (70,000–140,000)		nil	nil

In this table several things are of significance. In the first place, water gets through from the blood into the anterior chamber with the greatest of ease; proteins, with their gigantic molecules, hardly at all. In the second place, all the other diffusible substances get through comparatively slowly into the anterior segment, and with much greater difficulty and much more selectively into the posterior segment. In general terms the rate of entry is governed not by molecular size, as in physical diffusion, but by the chemical nature. Thus lipoid-soluble substances get through most readily, nitrogenous substances with the greatest difficulty. That some physical basis exists is suggested by the fact that within each group of substances the retardation varies to some extent with the molecular size—ethyl alcohol passes more quickly than the sulfa drugs, the monosaccharides more quickly than the disaccharides, urea than penicillin, and so on But by and large, a physical differentiation does not apply. Here we see an unusual delay in the passage of all molecules; an equality of the rate of passage of molecules of different size (when sodium and glucose enter at much the same rate); a block to the passage of nitrogen-containing molecules (whereby amino acids enter more slowly than glucose, the molecule of which is twice the size—or penicillin lags behind sucrose); and a facilitation of lipoid-soluble molecules (whereby the rate of penetration of sulfapyridine is over 20 times that of sucrose although the molecule is only slightly smaller, or the translation of urea to the larger molecule of thiourea increases its ease of passage five times). Clearly the passage is not on a physical basis but to a large extent is determined chemically. It is important also that synthetic substances, such as trimethyl glucose, which do not participate in metabolic activity in vivo, enter at the same rate as corresponding natural substances so that the process of transfer in their regard, at any rate, does not seem to be a secretion.

In the posterior segment of the eye this tendency is more accentuated. The chemical differentiation is greater and, what is more interesting, a regional differentiation exists. Thus we have found that sugars and thiocyanate enter throughout the whole of the circumference of the posterior segment while sodium and chloride enter in significant quantity only from the ciliary region. This, as we shall see presently, is important, but in the meantime we may note that in the posterior segment not only is the barrier less permeable and more selective, but for some substances, such as salt, is regionally selective.

Let us compare this with what happens in the body generally. As a working concept the capillaries may be considered as a meshwork of thin, platelike endothelial cells placed edge to edge to form a mosaic, the opposing edges being made tight by an intercellular cement substance of calcium protein-

ate, except for the presence of pores. In the extremities the tissue fluids contain some 0.5-percent protein; in the liver and intestines, 50 percent of the plasma proteins escape; in the intraocular fluid (and in cerebrospinal fluid) there is only a trace (0.02 percent). We may take it, therefore, that there are some pores in the intercellular spaces of the capillaries of the extremities of a diameter up to 38 Ångstrom units (the equatorial diameter of the plasma proteins); a large number in the liver and intestine; and only an exceptional one of this size in the capillaries of the eye. In the body generally, however, molecules smaller than this pass through the intercellular spaces of the capillary walls with ease—sodium, potassium, chloride, nitrate, and urea almost as easily as water, calcium, magnesium, and glucose with only slight delay—and even such large molecules as inulin comparatively easily. That is a physical passage by diffusion mainly through inactive intracellular spaces. The delay experienced by all molecules in traversing the ocular capillary walls and the differential retardation of molecules on a chemical basis can only, I think, be reasonably explained by a transference essentially through cell bodies instead of through their interspaces. This, of course, is not dialysis but something more subtle, discriminating, and apparently purposive.

A word now as to the regional differentiation. The blood-aqueous barrier in the anterior segment must be the uveal capillaries. In the posterior segment of the eye we have seen that there is a greater over-all difficulty in transit, more chemical differentiation, and in particular the block to sodium and chloride is very effective. We know that, when the retinal arteries are blocked, the inner layers of the retina behind the equator die, but anterior to the equator the entire thickness of the retina can be nourished and maintained in health from the anterior ciliary vessels. The deduction we may tentatively draw from this is that in the posterior segment of the eye, transudate from the choroidal capillaries does not reach the inner retinal layers, in quantity at any rate, so that fluid traffic into the vitreous in this region is essentially from the retina; in the preequatorial part of the vitreous chamber, on the other hand, traffic will be from the retina and choroid; and in the most anterior part, from the ciliary body. Posteriorly, therefore, where only the tenuous internal limiting membrane of the retina separates the tissues from the ocular cavity, the nature of the fluid bathing the vitreous will be determined essentially by the retinal capillaries.

This opens up a very interesting analogy between the permeability of the capillaries of the retina and those of the central nervous system. We know that all the capillaries of the body except those of the central nervous system are stained by acid dyestuffs such as trypan blue and allow their passage freely through their walls. Palm has recently shown that the same peculiarity applies to the retinal capillaries, for neither the endothelium of these capillaries nor the tissues of the inner retinal layers take on such a stain. It is obvious that the block here is the capillary walls. It is also interesting that the same deficiency of sodium chloride is found in the cerebral tissue-fluid as we have found in the vitreous. It would seem that the retinal capillaries have the marked peculiarities of the capillaries of the central nervous system which have been shown to differ widely from those of the rest of the body.

Let us turn now for a moment to the concentration of the various constituents of the intraocular fluid. It is interesting that all its constituents are in deficit in comparison with the plasma with four major exceptions: (1) hyaluronic acid, which must be synthesized locally and secreted into the eye; (2) ascorbic acid, which in some species (including man) seems to be actively transferred from the blood to reach a high concentration in the aqueous; (3) lactic acid in the presence of the lens, presumably a metabolic product; and (4) salts. The excess of salt (sodium and chloride) in the aqueous in comparison

with the blood is, I think, real. I am aware that this has been questioned, but our chemical analysis has received confirmation from another point of view. By every method we have employed we find constantly that the osmotic pressure of the aqueous is higher than that of the blood plasma; and if the two are dialyzed across a collodion membrane, chemical and physical measurements show a transference of salt from the former to the latter. It seems, therefore, that while all other freely diffusible substances with the specific exceptions just mentioned are in deficit, the concentration of osmotically active salts in the aqueous humor is in excess of that in the blood: in its transfer energy must therefore be expended, that is, it must be secreted.

Studies of the most varied nature in other organs of the body have consistently failed to produce any evidence that the capillary walls act otherwise than as a simple filter; they may block substances but they have not, so far, been detected in the act of secreting any substance. We know that, in the posterior segment, salt enters essentially in the ciliary region, and the work of Friedenwald, so ably summarized in his recent Proctor lecture, suggests a mechanism which might form the basis of such an active process occurring in the ciliary epithelium.

In the formation of the intraocular fluid we are therefore led to the suggestion that throughout the vascularized tissues of the eye there is a peculiar and controlled transfer of materials through the cell bodies of the capillaries instead of through their interspaces as in the body generally, and superimposed upon this, presumably in the ciliary region, a secretion of osmotically active salt. It is quite possible and indeed probable that the ciliary secretion may embrace other substances than salts, but I know of no conclusive evidence as yet to prove this.

If the integrity of the capillary walls is impaired, of course, these conditions are immediately and fundamentally altered. This change, which occurs universally throughout the capillaries of the body, can be accomplished by toxic or chemical influences but is most easily seen in alterations of the pressure relationships. This property of capillary fragility (as opposed to permeability) can be seen if a capillary is closed at both ends and is injected under pressure with India ink by means of a micropipet; as the pressure is increased the India ink will spurt out through a few isolated spots between the epithelial cells even though no tears in the endothelium can be seen. When the pressure is reduced and the circulation allowed to resume, these particles remain as localized collections outside the capillary walls and flow is resumed with permeability unimpaired. On paracentesis of the eye the reverse pressure relationship is seen, for the sudden lowering of pressure outside the capillary walls allows the passage of a protein-rich fluid wherein all the diffusible constituents approximate those of the plasma to form the plasmoid aqueous humor which is a simple filtrate from the blood; the proteins and all the diffusible substances increase, except the chlorides which diminish. In this case the ocular capillaries revert to the mechanism of the capillaries generally, and about this mechanism, which is universal throughout the body, we need not concern ourselves further.

Let us turn now to the drainage of these fluids. From experiments with heavy water, first carried out by Kinsey, Grant, and Cogan in Boston, we know that there is a full and free transfer of water in both directions across the capillary walls, just as occurs throughout all the bodily tissues, determined by the kinetic energy of the molecules involved; half the aqueous of the rabbit, for example, is replaced every 2.7 minutes—that is, there is a transference into and out of the anterior chamber of about 50 cu. mm. per minute. In addition to this there is a through-and-through circulation by way of the canal of Schlemm and the aqueous veins. This, unlike the general metabolic interchange, is not a process of diffusion but an undifferentiated flow in bulk allowing free mechanical exit to com-

paratively large molecules. This has been shown experimentally in my laboratory and also by a number of investigators using various techniques, and has been confirmed by the observation of the exit-flow through the aqueous veins in the human eye; the unanimity obtained by these results is striking. It would appear that in the normal eye approximately one percent of the fluid in the anterior chamber drains away per minute, a flow amounting in the normal human being to some two cu. mm. per minute.

We have now come to the point when we might venture to clothe these facts with some integrative philosophy. It may be asked, what is the purpose of this relatively complicated mechanism which we are postulating? Presumably it is concerned with making the eye a useful optical organ for which purpose two desiderata are necessary—optically clear media and an internal pressure sufficiently high to keep the globe a relatively rigid optical system. The peculiar impermeability of the ocular capillaries can be construed as a teleologic adaptation to maintain the ocular media optically clear and homogeneous. Transparency is maintained by excluding substances from the aqueous, but the deficiency of sugar, urea, creatinine, amino acids, and proteins amounts to about 4.5 millimols per liter. This has to be made up. An essential function of salts in the body is to maintain osmotic flow and equilibrium throughout the tissues. By a secretion, containing among, perhaps, other constituents, salts, this is made up and more than made up, so that the pressure in the eye is determined as a hydrodynamic steady-state by the capillary pressure plus an excess of osmotic pressure. And a slow outflow is provided, allowing a leak at the angle of the anterior chamber, so that the actual pressure in the eye is less than this pressure-head; and a safety-valve mechanism is provided so that the pressure does not get out of hand.

Finally it may be useful to consider what may be the practical bearing of this on the variations of the intraocular pressure found clinically. Obviously it may be disturbed by at least four factors: (1) An upset of the secretory activity involving in the first place osmotic changes; (2) a change in the permeability of the capillaries allowing the formation of a filtrate; (3) a change in the hydrostatic blood pressure, becoming effective either at the arterial ends of the capillaries when a rise in blood pressure will involve a rise in ocular tension or in the venous capillaries when an increased flow will encourage reabsorption of fluid and bring about a fall of ocular tension; and, finally, (4) by a blockage of the drainage channels which, by embarrassing the safety valve, will lead sometimes to a cumulative rise of pressure, sometimes to a strangulating crisis depending on other events in the eye.

About the effects of an upset of the secretory mechanism we know nothing; that is a problem full of enticement but equally full of difficulty. About the effects of vascular disturbances we know more. So far as local events are concerned, the effects of a rise in the capillary pressure on the tension of the eye have been elucidated. We also know that local stimuli have a generalized vasodilatory effect throughout the entire uveal tract through the mediation of axon reflexes so that dramatic results may follow insignificant stimuli. The massive and widespread vasodilatation, associated with increased permeability and edema, that may result therefrom constitutes the picture of acute congestive glaucoma. We also know that an increase of flow through the venous capillaries tends to lower the intraocular pressure; this action of eserine and pilocarpine, which cause such a dilatation and even open out new functional capillary districts, I think accounts for their hypotensive action often as much or sometimes more than their mechanical miotic effect. But about the central control of the local vascular system we know much less. Clinical observations with, it must be admitted, a slender experimental background suggest that neurovegetative, endocrine, and psychosomatic influences play an important part in its regulation; and

clinical and experimental facts relating to the diurnal pressure variation, the existence of a regulating mechanism, and the interdependence of the circulatory events in one eye with those in the other, whether determined by chemical or mechanical stimuli, strongly suggest the presence of a controlling center in the central nervous system, presumably in the upper brain stem or hypothalamic region; but the whole of this subject awaits experimental exploration.

About the effects of deficiencies or difficulties of drainage we are more fully aware; and probably because they are more obvious and amenable than the others to dramatic relief by treatment, I think we often attach undue importance to them. We know that a blockage of the angle of the anterior chamber seems frequently to be a precipitating cause of an acute congestive glaucoma. But it is equally important that a similar crisis may occur with the angle open as is seen, for example, in acute hypertensive uveitis. In this condition, if the accompanying vasodilatation and edema can be mitigated by control of the inflammation, the tension may fall. And after operation the tension may fall even though the angle, both in the operative area and elsewhere, is still gonioscopically blocked, suggesting that in some cases the hypotensive action of surgery may act by cutting short a vascular crisis rather than by opening up new drainage channels.

Similarly, in simple glaucoma we suspect that in a large number of cases there is some subtle hindrance to the exit channels of the intraocular fluid. But at the same time, in this disease, the outflow through the aqueous veins may be apparently at approximately the normal rate. Moreover, our everyday experience, that the normalization of pressure, either pharmaceutically or surgically, frequently does not prevent the evolution of the symptoms of this disease in their characteristic remorseless course, points to the fact that the whole philosophy of such cases cannot lie within the confines of the angle of the anterior chamber. Blockage of the drainage channels is certainly an adjuvant factor, but other mechanisms are as certainly operative; and these still require much exploration. For example, the state of capillary instability, found so commonly in cases of simple chronic glaucoma, and the lack of vascular compensation in conditions of stress, as seen in some provocative tests, are suggestive of an underlying fault in the capillary circulation, perhaps the same underlying fault which at the angle and the optic nervehead determines sclerotic changes.

The danger, of course, in studying so vast a problem is that in trying to unravel its intricacies we tend to become so specialized, each in our particular pursuit, that a broad and comprehensive view of the whole becomes increasingly difficult. Va ular events monopolize the attention of t.is investigator, the angle of the anterior chamber of that other. Such indeed is the tendency with the ever accelerating growth of ophthalmology in all its aspects—and indeed of all knowledge. Twenty-five years ago life was easy; today the physiologist, the chemist, the physicist, the mathematician, and the clinician all jostle each other in the market place, each advertising his own wares in his own peculiar language. To make advances in knowledge, specialization on minutiae is undoubtedly necessary; but we must beware lest, in the expanding sphere of thought, each individual discipline moves steadily away not only from a unifying and coördinating philosophy but from cognizance of each other, so that the value of each is vitiated by the exaggeration of its devotees, and its contribution to the solution of the problem as a whole is lost. For the subject of this lecture a comprehensive solution is yet far away, but insofar as it is an attempt to integrate some aspects of the problems concerned, it may perhaps be not without some value.

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CIRCULATORY ASPECTS OF THE GLAUCOMA PROBLEM*

The Second Mark J. Schoenberg Memorial Lecture

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The opportunity to deliver the second Mark J. Schoenberg Memorial Lecture brings to me a double honor. First, is the privilege to pay his memory respect; second, the privilege of associating my name through all time, not only with his, but also with all those who by these lectures perpetuate his accomplishments. His greatness of character has touched with stimulating effect all who knew him.

It is my purpose to discuss certain mechanical aspects of ocular circulation, which it seems to me can be brought together at this time not only because they include phases of our work in which Dr. Schoenberg was interested, but also because an effort is now in progress, through national and local committees† to assemble many of the loose ends which may help us to a clearer view of the symptom complex which we call glaucoma.

It is proposed to discuss phases of problems which have come to my attention through my own and my colleagues' ordered studies.

One must not lose sight of the fact that the word "circulation" may not refer solely to that of the blood-vessel system. It has been employed in referring to lymphatic channels and by Cushing,[1] under the heading of "the third circulation," to describe the cerebrospinal-fluid system.

There is a similarity between the cerebral and intraocular-fluid circulations. The word "circulation" in this sense is, of course, used broadly and was thought by some to be more comparable perhaps to the ebb and flow of a tide, its movements varied by depletions and excesses through tissue demands. Modern studies were necessary to prove a continuous flow from source to outlet.

The intraocular fluid has, to my mind, a major and a minor circulation. The lesser circulation is that of the aqueous chamber, the greater that of the vitreous. Combined they may be called "the fourth circulation."

I suspect the aqueous metabolic interchanges are less massive, although there may possibly be a greater rate of flow than there is in the greater circulation. I believe we should think of the vitreous as dynamically active. We might call it the liver of the eye because of its diverse storage of metabolites.

Perhaps the physiologic course of the fourth circulation would be: arteries through capillary endothelium, to aqueous and vitreous chambers, then posteriorly through the perivascular drainage spaces‡ and anteriorly through the escape exit of the canal of Schlemm, both to mix with venous blood.¶

It is conceivable that the posterior perivascular drainage may mingle with the cerebrospinal fluid of the vaginal space but our data for this idea seem to be insecure. There is evidence that certain bodies are

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† The work of the committee on standardization of tonometers; the work of the committee on the classification of the glaucomas; various tonometer testing stations; establishment of numerous glaucoma clinics.

‡ Priestly Smith[2] established that 2 percent of the outflow was by the posterior route. It would seem to me that 75 percent would be more reasonable in view of our modern ideas of vitreous function as a storehouse for retinal fuel and possibly waste products.

¶ It would seem probable that the vitreous may even receive certain of its constituents from the choroid. This is obviously so in pathologic studies, when we note opacities of the vitreous associated with the appearance of choroidal lesions.

passed from vitreous to orbital tissue. The question of the ultimate avenues of posterior drainage is definitely controversial. The metabolic constitution of fluid at any point in the fourth circulation would, of course, show local variations as it does in blood in accordance with local supply and demand.

Such an apparently static nutrient and waste concentration might indicate that the fourth circulation is designed only as an accessory for tissues of a low metabolic rate but we know that this is, in an overall sense, not so.

The interrelation of glucose interchange of vitreous and retina alone indicates that it may function as part of the retinal nutritive activity.[3] We realize that the actual volume of retina having a high metabolic rate is supplied on its outer face by the active blood bed of the choriocapillaris and that its inner face is also in contact with a relatively greater volume of vitreous.

The characteristics of a reversible elastic gell permit fluid transfer. This indicates that material amounts of nutrient and waste can be interchanged between retina and vitreous. The posterior drainage could thus be more active than past workers have indicated.[4] We need not discuss the properties of the vitreous as a gell and its many metabolic functions. Such studies have not been included in my own investigations.*

If we ask ourselves what are the metabolic demands placed upon the aqueous humor, we must admit that our answer is hypothetical. The cornea receives some benefits in a nutritive sense but the circumcorneal vessels must be a major supply source and there is a material absorption of oxygen through its exposure to the air. The iris, having its own vascular system, is relatively independent in maintaining its own support. All points considered, it would seem that the vitreous or greater portion of the fourth circulation should receive more attention. I should like to refer to a feature of vitreous structure which may even be quite active physiologically, and more active when pathologic conditions arise, I refer to fluid interchange.

The embryonic system of vessels, which is normally observed before birth, leaves behind infinitely fine fiber strands, that may be looked upon as cleavage planes or avenues of interrupted vitreous continuity. Experiments conducted by me in 1931[5] were suggestive that certain stains injected into the retrolental space were carried from the eye through the perivascular space† regions of the optic nerve and that they passed through the vitreous along lines strongly suggestive of the idea of fiber strands, cleavage planes or channels.‡ This impression is also gained in those cases of rupture of retinal veins when we see an irregular funnel-shaped formation of the escaped blood from an apex at the disc outflaring toward the lens. Active hyalitis sometimes shows a similar arrangement of inflammatory products and also is suggestive of orderly escape paths.

Mere cleavage planes of lessened resistance through the vitreous would suffice for the flow of fluid, the migration of mobile tissue cells, or even for the direction of growth of newly formed vessels.

Our present interest lies in the possibility that under pathologic conditions, the aqueous element of the vitreous might be gradually increased in the deeper parts of the gell, to be released by relatively sudden gushes

* The gell properties of the vitreous, particularly its changes in volume in response to fluctuations of the acid-base balance, have, in spite of elaborate studies, not advanced our understanding of the mechanism of intraocular pressure changes.

† My studies were made on animals[5] and human beings.[6] The literature dealing with our understanding of posterior drainage was published in 1930.[22] It gave credit to other workers for ideas similar to those presented at this time.

‡ I appreciate that when the acid-base balance of the vitreous is artificially disturbed, fibrillar micella[7] appear, with their long axes at right angles to the posterior lens capsule. We can confine our consideration to vitreous of undisturbed chemical balance, however, and still find evidence of retinal vessel strands. All other experimental methods of studying posterior drainage flow would seem to lead to false conclusions.[8]

through the cleavage planes to the perivascular lymph spaces which drain through the optic nerve.

This condition, with high pressure, can arise in the presence of relatively normal appearing vitreous which is relieved by a gushing forth of fluid and has been seen by all of us when performing a posterior scleral trephination.

As the opening is completed, a very considerable amount of fluid may eventually spurt from the vitreous chamber followed by the appearance of the apparently healthy gell. One can assume that, when the posterior drainage mechanism is obstructed, the iris-lens diaphragm advances, giving rise to the picture of shallow-chamber glaucoma.

The fact that the vitreous vessel remains sagged downward in adult life, would add to, rather than detract from the idea. The influence of gravity on the dependent regions of the vitreous would encourage a pool of the aqueous element below and would require a more elaborate system of escape than would the superior regions of the vitreous.

The vitreous is, according to Duke-Elder,[9] normally in its maximum stage of turgescence in healthy eyes and we must realize that gells act relatively slowly in transmitting water from one region to another. If this is so, acquisition of aqueous must be balanced by an equal escape and, since capillary dilation means increased permeability, we realize that the entire mechanism must be in constant activity.

Large nutritive demands upon the vitreous, although intimately related to similar demands upon the retina, are exceedingly difficult to study or demonstrate. The possible relation of vitreous volume to choroidal volume may seem more obvious.

The choroidal blood bed, representing as it does a much greater volume than the retinal, projects its dynamics into the problem of glaucoma. Moreover, we think of the choroid as a loosely woven mesh of thin-walled vessels in a pialike reticulum which is so designed that there is little structional restraint on active dilation and contraction of the vessels. It is even possible that the scattered muscle fibers of the choroid may be able to modify the gross thickness of the choroid as a whole. On the other hand, blood volume in the choroid may be varied by systemic changes or by a locally acting mechanism.[10]

It has long seemed to me that we gain a very artificial picture of the form, and hence the functions, of the choroid by the study of the usual histologic preparations. An uncompleted investigation into this question has lent evidence to indicate that the relatively thin appearance of the choroid, which we study microscopically, is in part due to the fact that the standard techniques of enucleation drain most of the blood from the eye.

To demonstrate this, a study was performed on a number of cats and monkeys.*[11] One eye of each animal was enucleated by obstructing the escape of blood of all vessels by the use of the actual cautery or by ligation. The technique was so successful that the orbits after enucleation were perfectly dry and there was no evidence of escaped blood on the globe. The fellow eye, used as a control, was enucleated by the usual technique of dividing tissue and vessels with scissors and scalpel. Both eyes were immediately placed in formalin for fixing and the usual and identical technique was applied to each eye in preparation for histologic study.

The thickness of choroid was measured in cauterized and control eyes only in the region where the macula was visible in the section and where the structures had not been torn or disarranged by the microtome. This precaution was taken in order to be sure that comparable regions of the choroid were measured for thickness.

To cite one example, the eye of a Sooty Mangabey monkey was studied. The average

* Rhesus and Sooty Mangabey monkeys.

measurements of the thickness of the choroid at the macula in four sections of the control eye, as measured with an ocular micrometer were 0.18, while the average thickness of four cautery-enucleated eyes was 0.273.* Thus, the choroid of the eyes removed without blood loss was 50 percent thicker. Moreover, the larger choroidal vessels were more rounded in cross section than oval, as is usually seen.

It is obvious that such a study is far from flawless in many respects. Yet its implications seem significant. In the living eye, the choroid must be much thicker than indicated in any of our preparations. A relatively drained choroid, as compared to a turgescent choroid, would represent a very great difference in the volume of the intrascleral chamber between these extremes.

A sudden depletion of the choroidal blood bed would be accompanied by a compensatory increase in volume of the vitreous through acquisition of the aqueous element. If this compensatory effect were over-sufficient, a rise of ocular tension would result but only if there was a derangement of the posterior drainage system. We must consider whether such violent variations of choroidal thickness can occur.

The interrelation of the clinically plotted[24] angioscotoma and the mechanism of the perivascular-perineural space has been a help in directing the management of glaucoma cases. Plotting the macula wedge as an index to prognosis and time of operation has been particularly helpful. It would seem reasonable, therefore, to conclude that there is modern evidence for the presence of a posterior drainage exit to support the incomplete evidence of the past.

After considering these features relative to the major division of the fourth circulation, it might seem reasonable to concentrate, in the future, on its physiology as an approach to the many problems of glaucoma.

It would be well to accept the idea of a "posterior" and an "anterior" glaucoma rather than to rely on a foreign differentiation of deep- and shallow-chamber glaucoma. We would do well to consider a specific and separate pharmacology for the posterior-chamber type; especially would it be well to consider those agents which modify the caliber of the uveal and retinal blood vessels.

A logical surgical technique for this type of glaucoma should be devised.† Surgical measures may involve the production of a minute area of choroidal atrophy by the application of beta rays, radium, or the thermophore, followed by a small scleral trephination with conjunctival flap over the atrophic area.

The blanching of the skin capillaries and the cerebral vascular changes occurring with emotional shock might conceivably be associated with similar changes of the choroidal vessels. In fact, Cholst[12] has presented experimental evidence of violent circulatory changes in the eye under shock conditions. These alterations provide a possible explanation for volume changes in the vitreous chamber. They might conceivably give rise to those attacks of acute glaucoma which are often associated with acute nervous shock.

Such ideas, of course, are highly speculative in spite of the oft-used phrase "sympathetic hormonal mechanism" and our generally accepted recognition of the fact that nervous shock often precipitates acute attacks. Repeated minor disturbances of sudden choroidal thickening with an inadequate posterior drainage might conceivably be the background for a chronic glaucomatous state.‡

* These are units of the ocular micrometer and do not refer to millimeters.

† It is interesting to note that the first successful effort toward the permanent surgical relief of hypertension was made by William Mackenzie (1830), who believed that vitreous changes influenced the site of increased pressure.

‡ The fact that appropriate fluids, deposited experimentally in the anterior vitreous, pass out of the eye through the posterior drainage system in 3 to 4 minutes (my own studies) may possibly have significance.

More detailed study of the choroidal vessels may shed more light on how this turgescence and depletion are brought about. In a group of studies conducted for a different purpose, a so-called capillary sphincter muscle was described.[10] Other workers[13, 14] have shown that like muscles in a number of tissues relax and contract under the effects of therapeutic agents.

We have shown histologic surface preparations suggesting that spasm of such capillary sphincters, when maintained over a long period of time, results in the formation of permanent strictures with greatly distended capillaries. These capillary sphincters have no relation to the hypothetical Rouget cells studied by Krogh.[15] In fact, many modern authors contend that Krogh's work cannot be duplicated. Moreover, the endothelial cells of vessels of the order of capillaries probably cannot swell and shrink[16] enough to modify greatly the volume of the capillary bed.

The passive injection and depletion of the immense choroidal capillary bed is thought by some to be controlled entirely from the arterial side in conjunction with venous activity of similar nature. In any event, the crux of the mechanism deals with the nature and force of capillary blood flow. The difference in the pressure gradient is sometimes accepted as an adequate explanation of capillary blood flow.

This question of forcing a fluid of relatively high viscosity through tubes as small as the capillaries* is not only debated by students of human physiology but also by students of plant physiology who are still trying to explain the origin of the terrific force which causes the sap to rise hundreds of feet to the tops of trees. It would seem, therefore, that a local mechanism is present which could conceivably give rise to sudden or gradual capillary distention and result in increased thickness of the choroid.

The history of efforts to define the form and functions of the perivascular spaces of the retina and optic nerve has been outlined elsewhere.[5] One is impressed with the similarity of these early studies to the efforts of the neuro-anatomists to investigate the cerebral perivascular spaces. At first, all was a confusion of artefacts created by techniques which were little understood.

The simple definition of the retinal perivascular spaces was, to my mind, first accomplished by the reliable technique of Wegefarth, one of Harvey Cushing's associates. He used a Prussian-blue method[17] which was radically different from the Prussian-blue methods previously employed.†[18]

Held[19] succeeded in devising a special stain and technique whereby he was able to study the minute histology of the cerebral perivascular spaces, and Kruckmann,[20] working in association with him, apparently accomplished the same result for the retinal spaces. As far as I know, however, Kruckmann's work has not been duplicated. In spite of this lack of corroboration, it is likely that his interpretations are correct. It has been pointed out elsewhere[22, 23] that there is other clinical and pathologic evidence of the existence of retinal perivascular spaces, and for other aspects of vitreous function.

Plotting of angioscotomas in all their physiologic and pathologic manifestations[22] has now been repeatedly duplicated by many workers all over the world. It would, therefore, seem justifiable to accept the hypothesis by which the studies were interpreted as reasonable. That hypothesis postulated primarily a perivascular space relation and an ultimate interruption of the retinal synapse.

Conclusions

1. The intraocular-fluid system may be looked upon as a fourth circulation (1. vas-

* On occasion so small as to permit only a single red cell to pass.

† I attempted to duplicate the technique of all earlier workers but my own studies of the retinal perivascular spaces confirmed the findings of Wegefarth.[17] Moreover, other workers (Magitot, Bailliart) have found obstruction to the retinal flow due to periphlebitis.[21]

cular; 2. lymphatic; 3. cerebrospinal fluid [Cushing]).

2. The vitreous may take a much more active part in the nutrition and in the pressure regulation of the eye than has heretofore been realized. There may be a large variation in the amount of the aqueous element of the vitreous during emotional shock and in general physical states.

3. The rapid passage of the aqueous element of the vitreous is probably greatly facilitated by "cleavage planes" within the substance of the vitreous. These cleavage planes or channels are the remnants of the embryonic vitreous vascular system.

4. There is considerable evidence to support the idea of a highly efficient and active posterior drainage system.

5. Marked variations in the volume (thickness-cross section) of the choroid can take place under a wide variety of conditions of systemic and local origin. Such variations, in the presence of obstructed posterior drainage, are capable of causing violent and rapid rises of intraocular pressure.

6. The capillary sphincter "muscle" of the uveal blood vessels provides a local mechanism which may be responsible for rapid changes in choroidal volume under general physical and psychologic stimulation.

7. These conceptions, supported by a great mass of experimental evidence, help to explain posterior (shallow-chamber) glaucoma and indicate the need for especially designed pharmacologic and surgical measures.

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GLOMUS CELLS IN THE HUMAN CHOROID AS THE BASIS OF ARTERIOVENOUS ANASTOMOSES*

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Harvey's thesis that the blood circulates from artery through capillaries into the veins is still the basis of our knowledge, although the last decades have shown that this truth is not without important exceptions. It has been known for 70 years at least (1877) that local short circuits may exist between artery and vein, which eliminate (more or less) the capillary system. So strange did this appear at first, that such an authority in the sphere of vessels as Thoma of Dorpat declared, in 1892, permanent arteriovenous anastomoses to be theoretically impossible, and Mall (1906) added that they would mean catastrophe if they should exist.

The careful investigations of Hoyer (1877), Grosser (1902), and Von Schuhmacher (1904), however, have proved that arteriovenous anastomoses exist physiologically in certain animal tissues, and that they can be opened and closed. Thus the blood stream takes the capillary path when the short circuit is closed, or runs through the opened arteriovenous anastomoses directly from the artery into the vein (figs. 1a and 1b). As a rule, the lumen of the arteriovenous anastomoses is changed quantitatively but efficiently, and a complete closure does not occur.

These arteriovenous anastomoses at first were virtually ignored by anatomists, physiologists, pathologists, and clinicians. Then, interest was aroused by the initiative of Hans Hawlicek, a surgeon, who realized the great importance of this double blood circulation.

Arteriovenous anastomoses were soon the object of careful research, the classical papers being by Clara (1927), Spanner (1932), Clarke and Clarke (1934), Masson (1935). Only the most important papers by these authors are quoted.

Arteriovenous anastomoses were found in many animals.

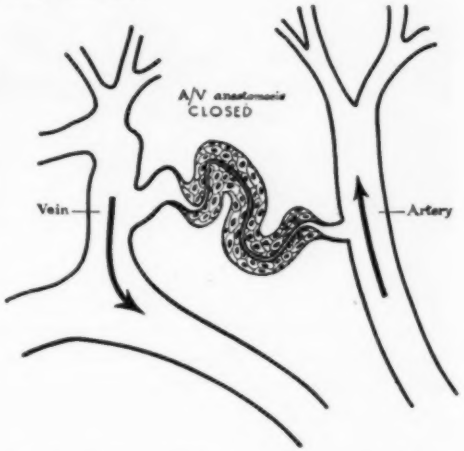

Fig. 1a (Loewenstein). The blood stream takes the capillary path when the short circuit is closed.

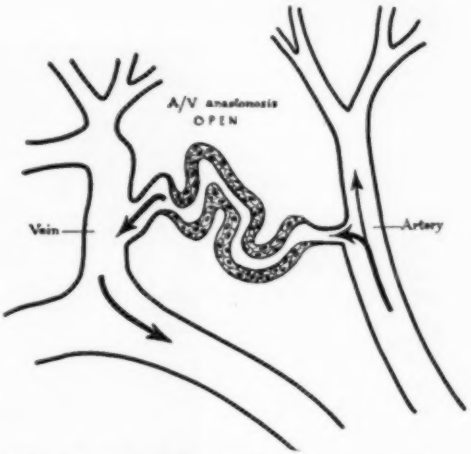

Fig. 1b (Loewenstein). When the anastomosis is open, the blood stream runs directly from the artery into the vein.

* From the Tennent Institute of Ophthalmology, University Glasgow (Prof. W. J. B. Riddell).

Fig. 2 (Loewenstein). Glomus cells in the arterial walls of a normal choroid. (Hematoxylin-eosin. ×300.)

In man, they were discovered in the pulp of the fingers and toes, the nailbed, the corpus cavernosum of the penis, in the glomus coccygeum, the villi of the intestine, and in other tissues. Masson associated the normally present arteriovenous anastomoses of the fingers with painful small tumors, enveloped in a rich muff of myelinated and nonmyelinated nerve fibers, which he called "glomus neurovasculaires" (1937).

The cells which are responsible for the mechanism of arteriovenous occlusion are of an epithelial character, and are placed external to the endothelium. They are found frequently in 4 to 5 layers, and are of very characteristic microscopic appearance. They are sharply outlined, the cytoplasm is clear, the nucleus is round and central. No membrana elastica interna is seen in the arteriovenous anastomoses.

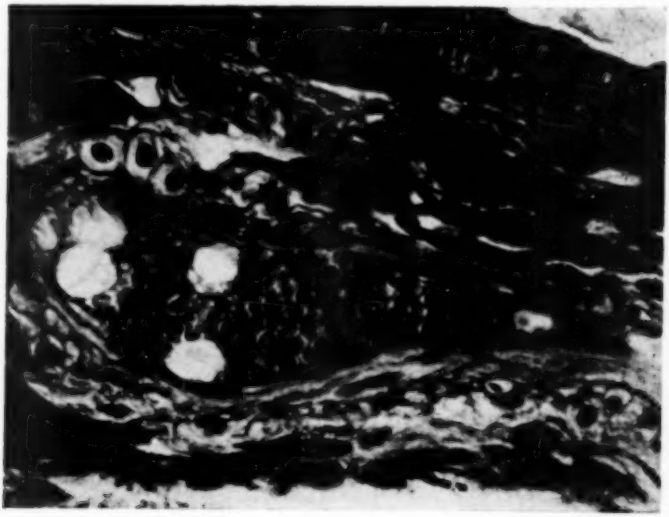

Fig. 3 (Loewenstein). Glomus cells in arterial wall of the choroid in a hypertensive case. (Hematoxylin-eosin. ×300.)

Although the arteriovenous anastomoses are more frequent in old people, Masson has found them in the fetus of 4 to 5 months, and in the newborn.

We are indebted to Clarke for the introduction of a technique permitting continuous observation of the living arteriovenous anastomoses under high magnification by a glass chamber implanted in the rabbit's ear.

The Clarkes thus discovered independent spontaneous contraction and dilatation of the arteriovenous anastomoses, which is faster than the arterial. The rate of contraction is different in arteriovenous anastomoses of close vicinity. Dilatation is as rapid as contraction.

Their autonomy is apparent and places the arteriovenous anastomoses into a special category in the whole circulatory system. Masson compares them anatomically and physiologically with the heart.

So far, arteriovenous anastomoses have been discovered in a restricted number of tissues only. I have observed, in the choroid of both normal and pathologic eyes, large clear cells of a certain uniformity. They were present in groups of medium- and large-sized choroidal arteries, and therefore in the middle and outer choroidal layers.

These cells (fig. 2) are polyhedric or round. In diameter they are between 10 to 20 μ sharply delineated, with a smooth, evenly dark-stained cellular membrane. They have a strikingly clear cytoplasm. The nucleus is central, darkly stained by hematoxylin, and without a visible nucleolus. Where these cells are found in groups they appear closely attached to each other, divided by the sharp cellular membrane. Their whole appearance is reminiscent, in fact, of epithelial cells (fig. 3).

Fig. 4 (Loewenstein). Fatty, swollen endothelial cells in an atheromatous choroidal artery. Here the nuclei are granular, pale, and most eccentric. Note the granular cytoplasm. (Hematoxylin-eosin, ×300.) (A) Hexagonal cells. (B) Bruch's membrane. (C) Choriocapillaris.

I have found them in choroidal routine, celloidin sections stained with hematoxylin-eosin, in Van Gieson, Masson, and Mallory stained slides. They are invisible in Weigert's elastica staining. They are located in the posterior pole area, and are absent in the anterior choroid.

I have also seen them in the intrascleral part of the posterior ciliary arteries of normal eyes. Their frequency is greater in hypertensive cases (fig. 3). They were especially rich in the posterior part of the choroid of an eye in which a metastatic malignant growth in the orbit pressed on the posterior portion of the sclera.

This histologic picture is very striking. The only pitfall might be the presence of huge swollen endothelial cells in choroidal arteries, the so-called pseudoxanthoma cells, in cases of malignant hypertension. But this "clear" cytoplasm is granular, the nucleus is pale and eccentric. Fat staining makes the differentiation complete (fig. 4).

The cells described correspond to those depicted by Clara, Spanner, Masson and others, and are called "glomus cells" or "epithelial muscle cells." I am unable so far, however, to reconstruct a complete picture of a clear-cut arteriovenous anastomosis with its arterial source, with the short circuit and the vein, like many of the other investigators of arteriovenous anastomoses. Technical difficulties vary in different tissues.

Fig. 5 (Loewenstein). Flat section of the choroid, posterior pole. Epithelioid muscle cells in the wall of a huge vessel. Note isthmus narrowing. (Hematoxylin-eosin. ×300.)

The glomus cells, both single and grouped, are visible in the sagittal sections of the choroid of the macular area, which has been embedded as flat as possible in celloidin, and sectioned in this way. The glomus cells are especially frequent where the arteries are tortuous and change the breadth of the lumen abruptly, sometimes from 1 to 4 μ (fig. 5). Some of these vessels with epithelial muscle cells have an inner elastic membrane; others have none.

Epithelial muscle cells are found at a

Fig. 6a (Loewenstein). Choroid in flat, Mallory stain, oil immersion. A rich mass of glomus cells in the wall of an artery. Difficult to distinguish between small, smooth muscle cells and epithelioid muscle cells.

Fig. 6b (Loewenstein). Choroid in flat, hemalum, oil immersion. Epithelioid cells.

certain distance from the endothelium, which itself is lined with the empty shells of cells (figs. 6a and 6b). These cells might be the circular smooth muscle fibers, cut eccentric to the nucleus. On the other hand, I am not sure whether these shells do not belong to eccentrically sectioned epithelial muscle cells.

The exact relationship between glomus and smooth muscle cells has not been determined so far. In the choroid both cell types might occur intermixed.

I have tried to find the structure of the arteriovenous anastomoses in choroid in bulk. For this purpose, the macular area of the choroid is first depigmented with potassium permanganate and oxalic acid; then the specimen is stained with a dilute hemalum solution for 24 hours and cleared in glycerin. The rich mass of nuclei is rather disconcerting and no counter staining therefore appears indicated.

In this way I was able to discover several groups of epithelial muscle cells (figs. 7a and 7b). They are grouped round a cystic empty space. The cells are of varying size, mostly polyhedric, sharply outlined; the cell membrane is sharp. Delineation between the single cells is well marked. The nuclei are dark, round, and generally central. These epithelial muscle cells stand out distinctly against the background of the smooth muscle fibers of the arterial wall. In a few instances only, there are more nuclei of the type described in a big cytoplasm, without being separated by cellular membranes.

These cells are at various depths—therefore the prospects of photomicrographic reproduction are poor. The dense background of nuclei adds to the photographic difficulties. These cell groups are similar, indeed, to all that has been demonstrated of arteriovenous anastomoses previously.

Generally, we must expect to recognize histologically the large dilated glomus cells only, while the contracted ones are oblong or spindle-shaped. There is little hope of identifying the latter two shapes in a stained bulk specimen. But even in sections, I was unable to discover anything apart from the epithelial form of the glomus cell. We have found, therefore, a part only, and possibly a small part, of the motive mechanism of the

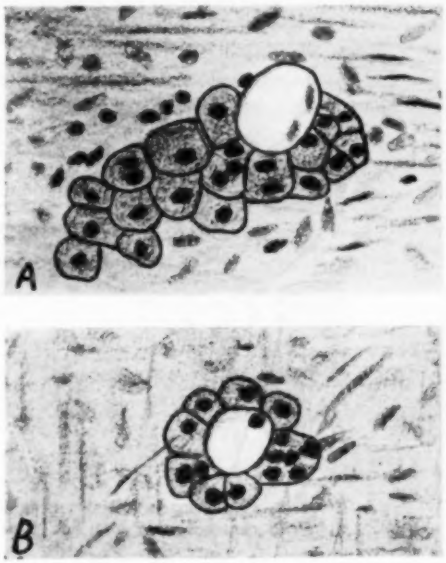

Fig. 7 (Loewenstein). Choroid in bulk, macular area, depigmented, hemalum, 24 hours, ×300, seen from scleral side. (A) Epithelioid muscle cells surrounding a cystic space. (B) Smooth muscle fibers of a middle-sized choroidal artery.

Fig. 8 (Loewenstein). Choroid in bulk, depigmented, teased, hemalum, 24 hours, ×300. One middle-sized choroidal artery shows narrowing at X. The muscle cells are dense, bigger, and darker at the place of contraction. A broad ciliary nerve branch crosses the vessel.

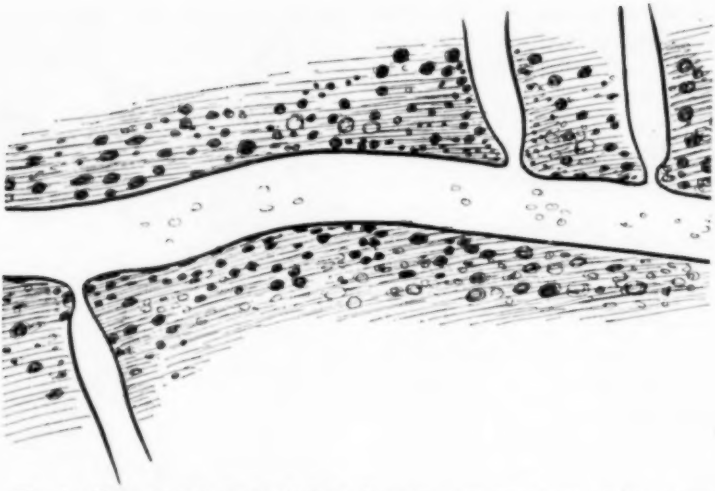

Fig. 9a (Loewenstein). Retina in bulk. Hemalum overstained and cleared. ×300. Sphincter contraction of branches. Note ganglion and glial cells in the superficial retinal layers.

choroidal blood circulation. That includes all previous research as well.

The investigation of the bulk choroid was continued by teasing the stained choroidal tissue with two needles, and clearing the shreds with glycerin.

I found, while following the course of a middle-sized artery, that the lumen 45 to

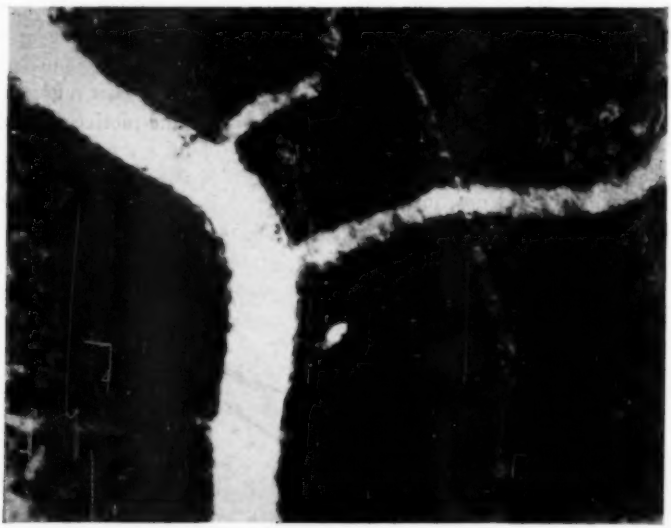

Fig. 9b (Loewenstein). Hypertensive retinopathy. Bulk specimen, hemalum, 24 hours, ×150. Sphincter contraction at the branching place of arterioles. Note retinal ganglion and glial cells.

50 μ diameter, narrowed down for a short distance to 15 μ and dilated again to the same width of 50 μ, that is a considerable contraction (fig. 8). It is interesting to observe that the muscle cells in the contracted area are denser, bigger, and appear darker than in the dilated part. We conclude that contracted smooth muscle cells in an arterial wall appear different histologically from the unstimulated ones.

Spastic changes in retinal arteries are supposed to exist and have even been observed in progress ophthalmoscopically. But no contraction of such degree has ever been seen ophthalmoscopically.

On the other hand, sphincter contraction has been described by Evans (1947) as an abrupt narrowing of certain retinal capillaries where they joined the vessel of the next order. I have shown this phenomenon at the Oxford Congress (figs. 9a and 9b) in retinal bulk specimens stained with hemalum.

The same sphincteric contraction is visible in the choroid (fig. 10) in bulk specimens. Blood transport in the district of arterioles,

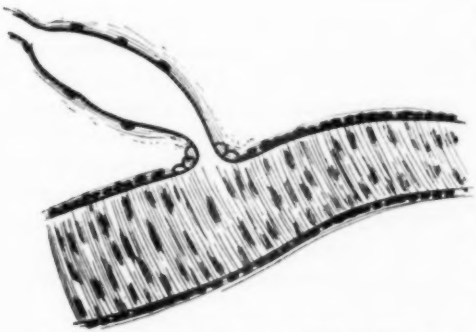

Fig. 10 (Loewenstein). Choroid in bulk, hemalum, 24 hours, overstained, ×300. Ring muscle fibers, no glomus cells, sphincter contraction.

metarterioles, and capillaries is far more complicated than was supposed. The brilliant investigations of Chambers and Zweifach (1946) have proved that a sphincter muscle is present at the union of a metarteriole and an "anastomosis" (not our arteriovenous anastomoses).

I have shown at the same meeting in Oxford (1946) swollen, granular, endothelial cells in capillaries, precapillaries, and ves-

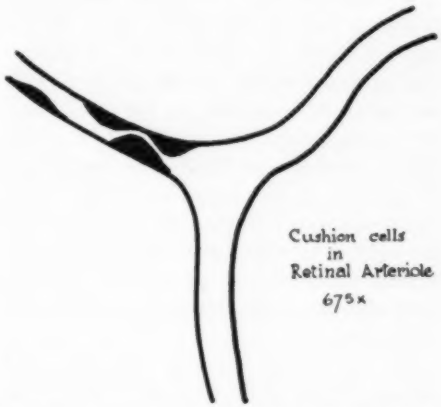

Fig. 11 (Loewenstein). Cushion cells in retinal arteriole. (×675.)

sels of unstained cleared retina in bulk at the point of branching arterioles and confluent vessels. I have suggested that these cells (fig. 11) swell and decrease, and regulate the local retinal blood supply according to need. I have not seen anything like arteriovenous anastomoses in the retina, so far.

We have seen, therefore, in the retina, two kinds of appliances to control the blood stream—the sphincter muscle and the swell or cushion cells, while we have found in the choroid epithelial muscle cells, the most probable base of arteriovenous anastomoses. The sphincter muscles of the choroidal arteries are similar to those found in the retina.

I am confident that further investigation will reveal other refinements in the regulation of the bloodstream.

It has been repeatedly stated that the choroidal structure is reminiscent of a corpus cavernosum. Filling and emptying of the biggest corpus cavernosum of man, that of the penis, is linked with existent arteriovenous of the arteriæ helicinæ.

The normal choroid is found sometimes histologically to be reduced to a thin tissue of 20 μ, while I have recorded not infrequently in the macular area of other equally normal eyes, a thickness of 200 μ.

We conclude that a regulator mechanism is able to dam up the blood and to fill the huge choroidal cavernous spaces, so impressive in flat sections or depigmented bulk specimens. It is credible, on the other hand, that arrangements are provided to evacuate this accumulation of blood in an emergency. Adaptation of the degree of filling of the cavernous system to the influx of blood and the outflow of intraocular fluid is necessary to keep the intraocular pressure at a certain level with inconsiderable and mostly regular oscillations.

One must not overlook that the most delicate tissues of the body are embedded in the hard, unyielding scleral capsule. These delicate tissues are exposed to the danger of being damaged by the increased tissue pressure, unknown mostly to soft body areas, unless a safety valve is provided. It seems that the arteriovenous anastomoses in the choroid offer sufficient possibilities to render innocuous a momentary influx of blood into the cavity of the globe. Quick reaction is therefore strictly indicated.

Such a regulation is very likely to be subject to nervous influence. Masson has, indeed, shown the highly developed and nervous muff enveloping the arteriovenous anastomoses. A similar network was shown recently by Nonidez (1942) in arteriovenous anastomoses of the sympathetic ganglion of the dog.

The nerve fiber system spread through the choroid appears very dense when studied in depigmented bulk specimens. So far, no histologic distribution of nerve fibers in epithelial muscle cells has been demonstrated successfully in the choroid. It is most probable that the function of the choroidal arteriovenous anastomoses opening and closing of the short circuits, are acting under nerve influence as are the other arteriovenous anastomoses (Clarke).

It seems different with vascular new growth in the choroid; for example, an angioma. This blastoma is seemingly not included in and subject to the free play of filling and evacuating of the blood spaces under nervous direction. We often find, therefore, increased intraocular pressure in such cases of angiomatous choroidal growth (Sturge-Weber syndrome).

It would be of great interest to observe a pulsation of the choroidal arteriovenous anastomoses resembling the spontaneous autonomous contraction found by Clarke in the rabbit's ear. I rather doubt whether the enlargement of slitlamp microscopy of the fundus will suffice. Clarke used high-power microscopy. But an eventual success will depend on the size of the pulsating area and on the intensity of the pulsation if it really exists.

There is a highly developed switchover system of the blood circulation in the tissues of the eye, basically different in conjunctiva, choroid, and retina. I have not studied so far ciliary body and iris.

The reserve vessel system in the conjunctiva has about 20 times the volume of that normally visible (Loewenstein, 1944), and will form the subject of a further paper by me. The retina, an infinitely more delicate and vulnerable tissue, has a proportionately delicate capillary mechanism in the form of endothelial swell cells, reinforced by the action of sphincters (Evans). The choroidal switchover system seems to be the most extensive.

I suspect that other devices for this purpose exist besides those described here.

Many puzzles remain unsolved and invite the investigators to continue their research in this direction. Last, but not least, it is possible that a pathologic finding might give a lead to the anatomist and physiologist. Arteriovenous anastomoses, glomus cells, respectively, are undoubtedly more frequent

in old people than in younger ones. They are found more often in hypertensive eyes than in normal ones. The process of causation remains obscure until now. It may be that their presence in the retrobulbar tumor case throws some light into the dark. More material must be collected.

I was unable, so far, to reconstruct the course of arteriovenous anastomoses from artery to vein, but I am hopeful that continued series of sections of depigmented choroidal tissue from the macular area will make it possible.

At present the first steps only have been made in this direction.

Summary

Large polyhedric cells are described in the periphery of large and medium sized choroidal arteries, with a central, round, dark nucleus, a clear cytoplasm, and a smooth cell membrane. These correspond to the epithelial muscle cells or glomus cells which are the basic elements of the arteriovenous anastomoses found in several tissues of animals and man. They are present in the posterior segment of the human choroid. They occur singly as a rule, in sagittal sections, but are found linked in flat sections and are present in epithelioid units in choroidal bulk specimens.

The choroidal glomus cells were found more frequently in hypertensive cases, and were numerous in a case of retrobulbar tumor with pressure folds.

The cells form part of the ocular tissue mechanism to direct the bloodstream to the areas of need, as do sphincter muscles at the branching place of arterioles in retina and choroid and the endothelial swell cells in the retina.

Arteriovenous anastomoses appear to be the basis of the choroidal corpus cavernosum. Rapid opening and closing of these short circuits is essential for the maintenance of the intraocular pressure and is dependent on the rich nerve fiber plexus demonstrated in other glomus growth.

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PANOPHTHALMITIS CAUSED BY ESCHERICHIA COLI COMMUNIOR*

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Escherichia coli is rarely the cause of ocular infections. Its presence in conjunctival cultures is in most instances a contamination. Eyre[1] (1897) found this organism in about two percent of cultures of normal conjunctival sacs, but in more recent studies by Khorazo and Thompson[2] (1935) it was present only three times in 1,122 cases. In rare instances it does produce inflammatory changes as evidenced by severe suppurative inflammation.

Français[3] (1935) reported two cases in which the organism was pathogenic. His first patient was a man aged 71 years, who, as a result of prostatic obstruction, developed an Escherichia coli cystitis three days following cataract extraction. A panophthalmitis occurred and the enucleated eye showed Escherichia coli. The second case was in a two-month-old child with a congenital dacryocystitis. The purulent exudate was filled with Escherichia coli. Catheterization of the nasolacrimal duct resulted in cure. The same author experimentally produced corneal abscesses, iridocyclitis, and panophthalmitis in rabbits and guinea pigs by the injection of Escherichia coli.

Sanyal[4] (1929) reported a form of conjunctivitis caused by Escherichia coli which was not uncommon in young men laborers of Calcutta. The infection appeared to be transmitted directly from the fingers. The typical attack began as an ordinary conjunctivitis and in a day or two assumed a moderately severe character. The lids became red, swollen, and tense, the upper overhanging the lower. The bulbar conjunctiva was swollen and infiltrated and there was intense injection of the palpebral conjunctiva which had a velvety appearance. There was a copious discharge from the eyes, at first mucopurulent but later of a purulent character. There was little pain except for a dull browache. Corneal ulceration occasionally followed.

Owens[5] (1946) recently reported a case of a severe corneal abscess caused by Escherichia coli which responded to local treatment by streptomycin.

The following is the report of a case of unilateral panophthalmitis caused by Escherichia coli communior and unsuccessfully treated with penicillin and sulfadiazine.

REPORT OF CASE

History. The patient was a 48-year-old housewife who had always enjoyed good health and had never had any previous ocular complaints. Twelve days before her first visit to the out-patient department, she experienced a stabbing pain in the right eye. The following day, the eye became inflamed. Two days after the onset of the illness, she consulted a local ophthalmologist.

His report stated that the lids of the right eye were swollen and red. The globe was under tension. The anterior chamber was shallow and the pupillary area was obstructed by an opaque hemorrhagic mass. The pupil did not react to light. Vision was limited to light perception. The temperature was 99.2°F.

Two hundred thousand units of penicillin in beeswax were administered twice daily

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and she also took 4 to 5 gm. of sulfadiazine by mouth each day. Urinalysis revealed a three plus reaction for sugar and injections of protamin zinc insulin were given. The eye gradually improved and she became able to distinguish form and color.

A sudden, sharp pain was again experienced in the eye eight days after the treatment was instituted and the lids became more swollen. On the following day there was fluctuation of the upper lid at the orbital ridge. Following an incision made into this area, there was escape of sero-sanguinous fluid and relief of pain. On the 12th day of the infection, she was referred to the clinic and admitted to the Institute of Ophthalmology.

Examination. On admission to the hospital, the vision in the *right eye* was limited to light perception with questionably accurate projection. The lids were greatly swollen, tense, and red. The upper lid was involved more than the lower. There was a slight sero-sanguinous drainage from the incision over the upper temporal orbital margin and a small amount of purulent bloody discharge on the lid margins. The lids could not be satisfactorily opened during examination because of the intense edema and pain.

The conjunctiva was deeply congested and chemotic. The cornea was steamy and of a grayish color. About 0.5 mm. of the peripheral cornea was relatively clear. The anterior chamber appeared shallow but no details could be seen. The intraocular pressure could not be estimated.

The vision of the left eye was 20/20. The globe and adnexa were normal.

General examination was noncontributory. At this time the fasting blood sugar was 86 mg. percent. Subsequent examinations and four-part glucose, acetone, and diacetic acid urine examinations were compatible with mild diabetes.

A gynecologic examination failed to reveal any evidence of a focus of inflammation in the pelvis.

X-ray studies showed some cloudiness of the right frontal and right ethmoid sinuses and some thickening of the lining membranes of the antra. An ear, nose, and throat examination showed no definite focus of infection. The chest X-ray film was negative. The mouth was edentulous.

Frei, Brucellergin, and tuberculin (1:1,000) skin tests and the blood Klein test were negative. The complete blood count was within normal limits.

Direct smears and cultures (blood-agar medium) were taken from each eye at the time of admission.

Treatment consisted of the instillation of 2-percent atropine sulfate solution to the right eye three times a day. Penicillin ointment (1,000 Oxford units per gm.) was applied to the conjunctiva and hot compresses were used three times daily. Twenty thousand units of penicillin, intramuscularly, one gm. of sulfadiazine, and one gm. of sodium bicarbonate were given every four hours. A sulfadiazine blood level of 10 to 12 mg. percent was obtained.

Three days after admission to the hospital there was no essential change in the appearance of the lids or globe except that a small white necrotic-appearing area about two mm. in diameter was noted in the sclera and conjunctiva in the four-o'clock meridian about three mm. from the limbus. On the sixth hospital day the lens had disintegrated and the anterior chamber was very deep. Evisceration of the right eye was performed on that day.

Laboratory studies

Morphologic characteristics. A moderate number of polymorphonuclear cells and Gram-negative bacilli were present in direct smears from the right lower cul-de-sac. The lid and conjunctiva of the right eye revealed a pure culture of Gram-negative bacilli which were nonacid fast, nonspore forming, and slightly motile. With the aid of standard biologic tests, the organism was identified as Escherichia coli communior. Lid and

conjunctival cultures of the left eye showed a nonpathogenic Staphylococcus albus.

Direct smears made from the eviscerated contents revealed Gram-negative bacilli. Pure cultures of Escherichia coli communior identical to those obtained from the conjunctiva and lid margins at the time of admission to the hospital were grown from cultures taken at the time of evisceration.

Animal inoculation. An emulsified culture of the isolated bacillus was prepared and the following animal inoculations were carried out:

Mouse. Adult white mice died within 18 to 24 hours following the intraperitoneal injection of 0.1 cc. of an 18-hour culture. Escherichia coli communior were recovered from cultures taken at autopsy of the mice.

Guinea pig. An intraperitoneal injection of 0.5 cc. was made, with no effect.

Rabbit. Adult white rabbits were used for intraocular studies. Injection of 0.01 cc. of an 18-hour culture of the organism into the cornea of a rabbit produced a fulminating panophthalmitis within 48 hours as did 0.05 cc. injected into the anterior chamber. The lesions in the rabbit presented changes in the globe similar to those found in the patient. When the cornea was inoculated by scarification with a needle which had been dipped into the culture or by instillation of the culture into the conjunctival sac, infection did not result.

Sensitivity to antibiotics. By standard in vitro bacteriologic methods, the organism was found to be resistant to penicillin but was markedly sensitive to streptomycin.

Pathology. Fixed sections of the specimen obtained at operation showed an acute inflammatory reaction, a few Gram-negative bacilli, and early organization of a hemorrhage.

Conclusions

Although very rare, this case demonstrates the possibility of Escherichia coli communior as an etiologic agent in panophthalmitis. It also shows the importance of obtaining direct smears and cultures from the conjunctiva as an aid in determining the cause of intraocular infections. Judging from the behavior of the transference of the organism to rabbits, it seems probable that this infection was metastatic.

The organisms were not sensitive to penicillin but were found to be sensitive to streptomycin. Had the nature of the infection been determined early, and an adequate supply of streptomycin been available, the infection might have been successfully combatted.

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INTRAORBITAL MENINGIOMAS

A Clinicopathologic Study*

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Until recently, intraorbital meningiomas have been almost exclusively a problem of the ophthalmologist. With the demonstration of an intracranial route of approach for their removal, intraorbital meningiomas now have come to be fully as important to the neurosurgeon as are meningiomas elsewhere.

Primary intraorbital meningiomas are comparatively rare; they have been recognized and removed surgically in 17 cases at the Mayo Clinic. Secondary, or invading intraorbital meningiomas occur more frequently.

The first report with tangible evidence of what may well have been an intraorbital meningioma was that of Scarpa[1] in 1816. He described an intraorbital growth which seemingly had its origin within the sheath of the optic nerve. This tumor was removed successfully without injury to the eye. A few years later, Wishart[2] described a similar growth in some detail.

Byers,[3] in 1901, collected from the literature of the 19th century reports of 102 intradural tumors which occurred within the orbit. Although his work was comprehensive, an accurate appraisal of the nature and the frequency of these intradural tumors was precluded by the then-existent confusion in the histopathologic identity of the various neoplasms. Most, undoubtedly, were gliomas and sarcomas.

Hudson,[4] in 1912, placed the classification of primary tumors of the optic nerve on a sounder footing in that he grouped them into three categories: gliomas, endotheliomas, and fibromas. With increasing recognition of the meningioma or endothelioma as such, reports of cases of intraorbital meningioma subsequently appeared in the literature with greater frequency. Goar,[5] in 1926, and Mayer,[6] in 1928, fixed the total number of intraorbital meningiomas described in the literature at about 40. However, whether the intradural tumors had had a primary origin within the orbit or whether they had extended into the orbit from an intracranial source had not been determined in many instances.

The origin of these tumors still is somewhat indefinite. Since the classical article on meningeal tumors by Schmidt,[7] in 1902, these growths have been thought to arise from clusters of arachnoid cells. Cushing and associate[8] pointed out that "from a histopathological standpoint, there is no apparent reason why the arachnoid layer of the optic nerve sheath should be any more exempt from tumefactions than the intracranial arachnoids."

It was the opinion of most of the earlier workers that the endotheliomas and psammomas of the orbit took their origin from the optic sheath or the sheath of Schwalbe.[9-11] The intraorbital meningioma on which Heed[12] reported was intimately attached to the pial sheath of the nerve, and it seemed that the growth sprang from this tissue.

Some of these tumors apparently arise within the optic sheath and then break through into the orbital cavity as pointed out by de Lapersonne.[13] Van Duyse,[14] in 1923, felt that his particular example was a tumor of peridural origin with secondary invasion into the optic sheath. Dandy[15] des-

* Abridgment of thesis submitted by Dr. Gogela to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Neurosurgery.

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cribed bilateral, collarlike endotheliomas which extended both anteriorly and posteriorly from their sites of attachment at the point of reflection of the dural sheath at the optic foramina. Cushing and Eisenhardt[8] stated that the favored point of origin of these tumors was unknown, but considered the "vicinity of the foramen" the most likely site.

Some investigators have suggested other sites of origin than the sheath of the optic nerve, or sheath of Schwalbe. Wiegmann,[16] in 1929, reported that he had removed an intraorbital meningioma. He concluded that it was "impossible" for the growth to arise from the optic sheath in view of the fact that the tumor lay outside the bellies of the muscle. Benedict,[17] in 1923, also removed a meningioma which was situated "outside the muscle cone," and Levkoeva,[18] in 1931, reported a "free-lying" intraorbital meningioma.

Levkoeva[18] concluded that the meningioma in his case had probably arisen from the "dura mater of the orbit." "However," he stated, "its development from the periosteum is not to be excluded." Others also have suggested a relationship of the orbital periosteum to meningiomas. Schreck,[19] in 1939, after studying 15 intraorbital meningiomas removed at the University of Heidelberg, concluded that these tumors arise not alone from the sheath of the optic nerve, but can occur "completely separated and free with the orbital tissues."

As was clearly pointed out by Cushing and associate,[8] meningiomas possess a tendency to expand along the lines of least resistance and force their way into "all anatomical crannies and pockets." This fact precludes critical evaluation of many of the so-called intraorbital meningiomas which have been reported in the literature. For example, the meningioma that Byers[3] reported, which had supposedly originated within the orbit, was found later at necropsy to have (very probably) extended through the intervaginal space into the orbit from its primary site along the olfactory groove. Cushing's series of 29 meningiomas of the olfactory groove included one meningioma which encroached on the intraorbital contents through the optic foramen.

Meningiomas of the sphenoidal ridge may cause unilateral exophthalmos and must be differentiated from intraorbital tumors. Elsberg and associates[20] also warned that tumors producing unilateral exophthalmos may have extended into the orbit through an enlarged superior orbital fissure or may have destroyed bone and penetrated into the orbit. However, other meningiomas, such as the suprasellar growths, which seemingly would be more likely to invade the orbit through the intervaginal space, do not do so for some "unaccountable reason."

Materials and Methods

Several fresh specimens obtained at necropsy were examined for possible sources of tissue which might give rise to meningiomas within the orbit. The contents of the posterior two thirds of the orbit, the optic foramen, and the orbital fissures were released en masse by a transverse vertical section just behind the globe. The blocks of tissue were fixed, imbedded, sectioned, and stained by routine methods with hematoxylin and eosin. A careful study of this material then was made with particular reference to the presence, within the orbit, of cells, tissues, and other structures characteristic of the intracranial meninges. Search was made for the typical clusters of arachnoid cells and psammoma bodies.

The major portion of the study was made on cases of meningioma. The number of cases studied will be mentioned with the results. At the outset, all intraorbital meningiomas were placed into one of two sharply and mutually exclusive categories as determined by findings at the time of operation or necropsy. The tumors designated as "primary" within the orbit were those which

formed within the orbit and did not extend to occupy a position within the orbital cavity from a primary source elsewhere. The group of secondary intraorbital meningiomas was composed of meningiomas which extend into the orbit from other sources. Selection of the cases in this latter group was determined by actual invasion of an orbital opening by the tumor, by actual presence of the extended mass within the orbital cavity, or by the presence of a hyperostotic dorsal orbital plate and measurable exophthalmos.

In an attempt to correlate the presenting signs and symptoms of the primary tumor with its intraorbital location, special effort was made to note its relationship to the various intraorbital structures. The secondary tumors were studied specifically to determine the route of orbital invasion and findings which would be helpful in distinguishing this class of tumors from the primary group on clinical, or other grounds.

Anatomic findings

As mentioned before, the retrobulbar intraorbital contents provided by several necropsies were examined for arachnoid cells or proliferations which could conceivably act as nidi in the formation of meningiomas. In every instance, clusters of arachnoid "cap" cells and small calcified psammomas were found within the meningeal sheath covering the optic nerve. However, similar formations were not observed along the course of other intraorbital nerves or vessels. Nor were clusters of arachnoid cells ever discovered free within the interstitial tissues peripheral to the sphenoidal fissure. The periorbita, or intraorbital periosteum, consisted of a heavy sheet of collagenous fibers and was devoid of lining cells of any sort.

Examination of a single longitudinal section through the optic nerve and its sheath often disclosed 15 to 20 fusiform clusters of 6 to 8 layers of typical, closely packed arachnoid cells. Small, deeply staining, cal-

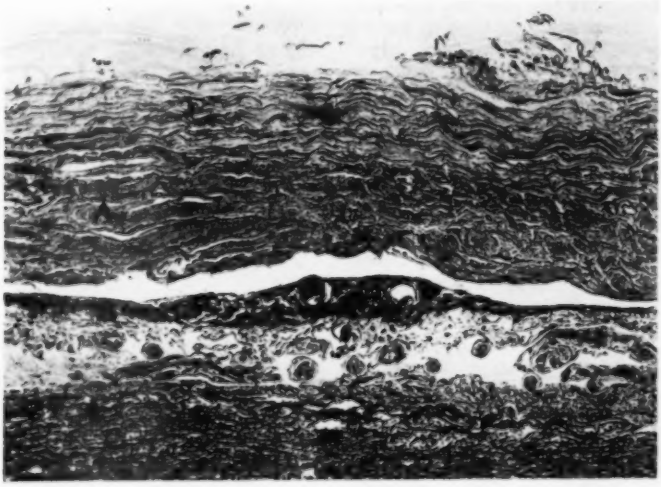

Fig. 1 (Craig and Gogela). Longitudinal section through a normal optic nerve and sheath illustrating clumping of arachnoid cells into a "cap"; (A) dura; (B) arachnoid cluster with psammomas; (C) optic nerve. The widened subdural space is an artefact (hematoxylin and eosin, ×90).

cified psammomas were frequently observed nestling within these groups of cells (fig. 1).

Clinical findings

Primary intraorbital meningiomas.

Primary intraorbital meningiomas have been recognized in 17 cases and treated surgically at the Mayo Clinic. The diagnosis was verified microscopically and a careful study was made at the time of operation to establish that they were primary intraorbital growths. Included in this group are the meningiomas taking their origin within the confines of the optic foramen and subsequently extending both intraorbitally and intracranially.

The primary tumors were placed into 1 of 3 groups: (1) The foraminal meningiomas; (2) the growths which arise from within the sheath of the optic nerve; and (3) those which did not seem to stem from the coverings of the optic nerve but which lay more or less freely either within or outside the muscle cone or were attached firmly to the periorbita.

The tumors were foraminal in location in three cases (fig. 2). In two of these they were bilateral. Nine growths enveloped the optic nerve or were firmly attached to its optic sheath, and the five remaining tumors appeared to arise from some source within the orbit other than the sheath of the optic nerve.

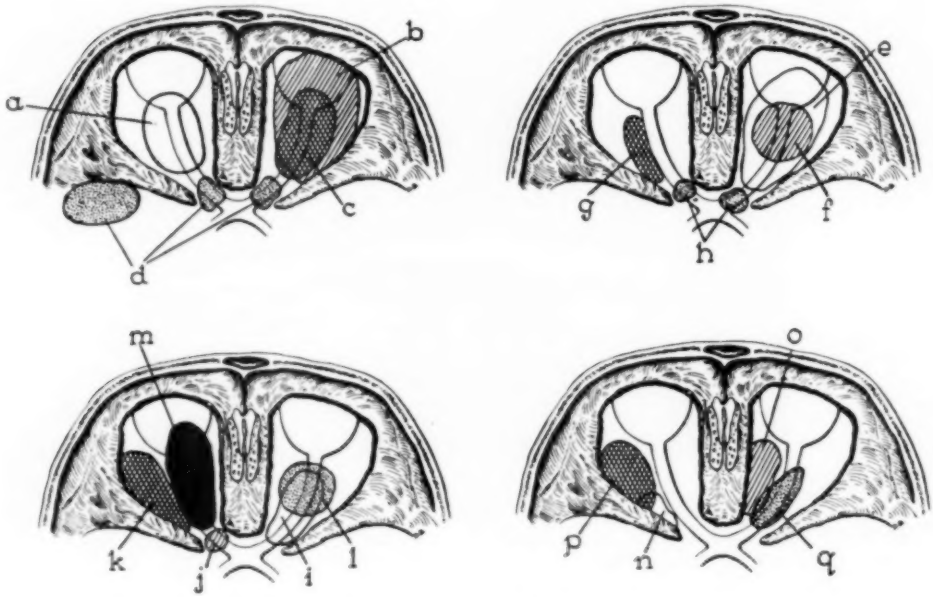

Fig. 2 (Craig and Gogela). (A to Q) Location and attachment of primary intraorbital meningioma in 17 cases.

Thirteen (76 percent) of the patients were females and four (24 percent) were males. A similar sex ratio was found in the cases of the secondary meningiomas also. The ages of the patients who had primary intraorbital meningiomas extended from 14 to 55 years; and the majority of the patients were in the late middle years of life. The average age of the patients at the time of examination was 41 years. However, in-

itial symptoms and signs appeared at an average age of 35 years.

The presenting signs and symptoms consisted of visual impairment, measurable proptosis, and headache. Either visual failure or proptosis, or both, were present in every instance. Headache was recorded in only five cases and was generally described as being mild and occasional. The site of the pain was usually supraorbital or retrobulbar.

The presence or absence of proptosis or visual impairment and the time of onset of the two appeared to be related to the site of the lesion. In the three cases in which the tumors were confined to the optic foramen, progressive loss of vision was the only presenting symptom. Exophthalmometric readings failed to disclose proptosis in any of these cases. Case 1 is representative of this group.

Case reports.

Case 1. A housewife, aged 30 years, registered at the clinic on November 11, 1938. The family and personal history were irrelevant. At the age of 12 years, the patient noted that she was beginning to lose vision in the left eye. The loss of vision in that eye advanced gradually but continuously to complete blindness. The patient felt well otherwise.

About 18 months prior to registration, she noted that vision in the right eye was beginning to fail. Six months after the onset of symptoms referable to the second eye, the patient consulted a physician who performed encephalographic, spinal fluid, and serologic studies, all of which gave negative results. A diet designed to determine an allergenic basis for the optic atrophy failed to bring about a beneficial response. Since the onset of visual failure in the second eye, the patient had had a general feeling of ill health, had become nervous and had lost 10 pounds (4.5 kg.).

General physical examination at the clinic disclosed a small, slight, white woman who appeared younger than her stated age of 30 years. Objectively, physical findings were normal with the exception of those relating to the eyes. Neurologic examination gave essentially negative results except for changes in the ocular reflexes secondary to the amaurosis.

Proptosis was not present, and the eyes rotated normally. The patient was completely blind in the left eye and was able to distinguish moving objects only in the temporal field of vision of her right eye. Ophthalmoscopic examination disclosed pallor of the left disc, grade 4, on a grading basis of 1 to 4, with temporal loss of substance, grade 2. The right optic disc similarly was extremely pallid and there was residual edema of two diopters.

Flocculation tests for syphilis and tests for possible lead or arsenic poisoning revealed nothing of significance. The blood sedimentation rate was 8 mm. in one hour (Westergren) and the concentration of protein in the cerebrospinal fluid was 30 mg. per 100 cc. Roentgenograms of the head, the optic foramina, the sinuses, and thorax showed nothing abnormal.

A diagnosis of an inflammatory or neoplastic chiasmal lesion was made and right transfrontal craniotomy was performed on December 8, 1938. On elevation of the right frontal lobe, dual, cufflike neoplasms were observed which encircled and compressed the optic nerves at the optic foramina. The tumors were dissected free and, because of some remaining vision in the right eye, the dorsum of the optic canal on that side was decompressed in the hope that there would be some restoration of function in that nerve.

The patient convalesced without incident and was dismissed from the hospital on the 13th postoperative day. Neurologic examination gave negative results at that time and findings on ophthalmoscopic examinations and examinations of the ocular fields remained unchanged. A few months after dismissal, the patient reported that she felt well and had noted some subjective improvement in vision in her right eye.

On microscopic examination the tumors proved to be meningiomas of a heavily calcified psammomatous character similar to that illustrated in Figure 3.

In this case, the tumors were slow growing and small and were situated so that any pressure they may have exerted was ineffective in producing exophthalmos.

In Case 2 the tumor originated within the sheath of the optic nerve. Visual failure and proptosis both were present.

Case 2. The patient, a nun, aged 35 years, registered at the clinic on March 21, 1947. Her chief complaint was progressively decreasing vision in the right eye during the five preceding years. The loss of vision had been almost total for a period of one year. Vision in the left eye was unaffected. Although her right eye had been feeling "heavy in the morning," she had failed to note any definite proptosis of the right eye. Except for a few sharp, right supraorbital headaches which were relieved with aspirin and rest during the preceding 18 months, the patient had felt well. The family and personal histories were noncontributory.

General physical examination revealed nothing abnormal and neurologic examination gave negative results except for depression of the light reflexes incidental to amaurosis. Vision was reduced to perception of light in the right eye and was normal in the left.

Exophthalmometric measurements disclosed prop-

tosis of 7 mm. on the right. Extraocular movements were normal. Extreme pallor and some loss of substance of the right optic disc were noted. The left eye was normal in all respects. Roentgenologic studies showed that the right optic foramen was smaller than the left and the bony collar was denser. Flocculation tests on the blood gave negative results.

The condition was diagnosed as right intraorbital tumor, possibly meningioma, and right transfrontal craniotomy was performed on April 9, 1947. The dura was stripped from the roof of the right orbit; both the dura and the roof of the orbit appeared normal. The meninges were slit along the sphenoid crest, as for exploration for an intracranial meningioma, and the right optic nerve was found to be atrophic and compressed at the optic foramen by a small bit of tissue extending intracranially from within the orbit. There was no evidence of an intracranial meningioma otherwise. Consequently, the optic canal was unroofed and the orbit was decompressed; there appeared to be some osteomatous thickening of the lesser wing of the sphenoid. The sheath of the optic nerve was opened widely and a mass of tumor was recognized to the right of the nerve. With a view toward preserving the optic nerve and the muscle cone, removal was necessarily incomplete. Postoperative convalescence was uneventful and the patient was dismissed from the hospital on the ninth postoperative day.

Four months later, the patient noted a "sensation of pressure" behind the right eye and was given a course of roentgen therapy. The exophthalmometer disclosed proptosis of only 2 mm. at that time. Vision in the right eye was nil.

On microscopic examination, the growth was found to be a meningioma of the meningotheliomatous type.

In some cases, proptosis is the chief presenting complaint. Case 3 is an example of this and of the type of intraorbital meningioma which bears no evident relationship to the sheath of the optic nerve.

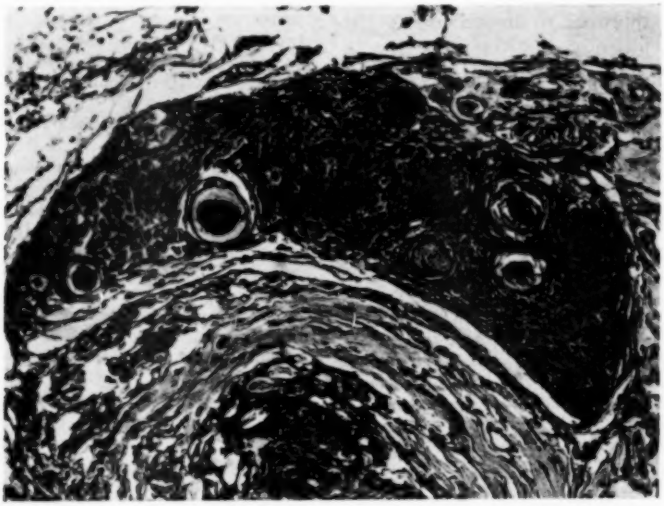

Fig. 3 (Craig and Gogela). Calcified psammomas within a lobule of evenly dispersed meningioma cells (hematoxylin and eosin, ×130).

Case 3. A white business man, aged 54 years, registered at the clinic on October 1, 1946. Four years previously, he first noted protrusion of the right eye and fullness of the upper lid. A short time thereafter, he consulted a physician who recommended roentgenographic studies of the sinuses and the orbit. No changes suggestive of a space-occupying lesion were found at that time, nor had such changes appeared one year later. In April, 1945, the orbit was explored elsewhere through an incision in the brow and a bit of tumor was removed for microscopic study. This was reported to be a meningioma.

The patient's only complaints at the time of examination at the clinic were prominence of the right eye and fullness of the right upper lid. He had no pain, no evident limitation of ocular movements, and no subjective visual impairment.

General physical examination gave negative re-

sults except for a moderate degree of obesity and mild hypertension. The systolic blood pressure was 150 mm. Hg and the diastolic was 96. Neurologic examination disclosed no abnormalities.

The right eyeball protruded forward and laterally and there was some slight ptosis of the right upper lid. A definite mass was palpable in the superior nasal quadrant of the orbit. When specifically tested for diplopia, the patient noted doubling of vision on looking upward and to the left. Vision was recorded as being 6/6 in the left eye and as 6/15 in the right. Flocculation tests on the blood gave negative results and roentgenologic studies of the head and orbit failed to suggest the presence of a lesion.

A right transfrontal craniotomy was performed under ether anesthesia on February 3, 1947. The roof of the right orbit was removed, and it was at once evident that the intraorbital contents were under increased pressure. When the capsule was divided and the intraorbital fat retracted, a flat tumor was found along the medial wall of the orbit. Because the mass was firmly adherent to the wall, total removal was not possible. Microscopic study of frozen sections made at the time of operation disclosed the growth to be a meningioma. On examination of the fixed specimen, the tumor was classified as meningioma of the fibroblastic type.

The patient was ambulatory on the third postoperative day and was dismissed from the hospital on the 11th postoperative day. At the time of dismissal, there was still considerable edema of the soft tissues of the right eye; however, the globe was in good condition and vision in that eye had not changed.

On reëxamination seven months later, the patient felt well but exophthalmos of 8 mm. and some ptosis of the right upper lid still persisted. Vision was recorded at 6/6 in the left eye and 6/10 in the right.

Comment.

With the exception of the alteration of light reflexes incidental to the atrophic changes in the optic nerve in some cases, neurologic examination gave uniformly negative results in all but one case. In this one case, pathologic neurologic findings were ascribed to coincidental multiple lesions.

In addition to routine roentgenographic studies of the head, special poses designed to demonstrate the orbital and the optic foramina to the optimal advantage were employed. Roentgenographic findings suggestive of a lesion in the region of the orbit were recognized in 6 of the 17 cases. Bony proliferation of the roof of the orbit or the wing of the sphenoid bone or in both sites was recognized in four cases. Two of these tumors arose from the sheath of the optic nerve and two from a source within the orbit but apparently not from the sheath.

SECONDARY INTRAORBITAL MENINGIOMAS.

The tendency of 148 meningiomas located in the region of the anterior fossa of the cranium to invade the orbit was studied. The tumors were classed into four groups according to the site of origin as reported at the time of operation (table 1). The largest

TABLE 1

TENDENCY TOWARD ORBITAL INVASION BY PRIMARY INTRACRANIAL MENINGIOMAS

Site of Origin	Total Tumors Examined	Invading Orbit	
		No.	Percent
Sphenoidal ridge	64	25	39
Olfactory groove	24		
Basofrontal region	16	5	31
Sellar region	44	5	11
Total	148	35	24

single group (64 tumors) consisted of tumors arising along the wings of the sphenoid bone. The site of origin of the remaining meningiomas was designated along the olfactory groove and in the basofrontal and the sellar regions.

The 44 sellar meningiomas include all those within and about the sella turcica. At operation, they were variously described as being "intrasellar," "suprasellar," "parasellar," or attached to the "crest of the sella."

Of the four groups, those tumors arising along the sphenoidal ridge displayed the greatest proclivity toward orbital invasion. Twenty-five (39 percent) of a total of 64 tumors presented clinical and surgical evidence of encroachment on the confines of the orbital cavity. Proptosis was present in every instance and was due to 1 of 5 various conditions: (1) Formation of an osteoma on the roof of the orbit; (2) destruction of bone and extension of the tumor through

the defect; (3) simultaneous formation of an osteoma on the roof of the orbit and extension of the tumor into the orbital cavity; (4) extension of the tumor through the orbital fissures; or (5) simultaneous extension through the optic foramen and the orbital fissures.

Sixteen (64 percent) of the 25 invading meningiomas which arose along the sphenoidal ridge compressed the contents of the orbit as a result of formation of an osteoma on the orbital roof and walls. Four tumors extended through an orbital fissure; two through defects produced by destruction of bone; two invaded the orbit through both an orbital fissure and the optic foramen, and one produced ocular symptoms by simultaneous formation of osteoma and invasion of an intraorbital tumor.

None of the meningiomas situated near the olfactory groove in this series evidenced any definite signs of orbital compression.

Of 16 basofrontal growths, five were encroaching on the orbit at time of surgical exploration. In three instances, the tumors invaded the orbital space through areas of destroyed bone. In the two remaining cases, the exact manner of extension of the growth was not determined.

Five of 44 tumors located in the region of the sella turcica were discovered to have extended to, and into, the optic foramen. In no case had extensive invasion of the orbital cavity proper occurred.

Of the 35 intracranial meningiomas secondarily invading the orbit 28 (80 percent) occurred in females. Fifteen (43 percent) of the patients were in the fifth decade of life.

All the invading sphenoidal ridge and basofrontal meningiomas produced proptosis, whereas the sellar tumors produced exophthalmos in only one case. Visual difficulties were complained of in approximately 80 percent of the cases of sphenoidal ridge and basofrontal meningiomas; whereas, in all five cases of sellar meningiomas, visual symptoms were produced.

There was a striking paucity of other neurologic complaints which would presumably have assisted in distinguishing these tumors from primary intraorbital meningiomas. Nine patients complained of headache; three noted failing memory; two perceived decreasing olfactory sensation; and one had fainting spells.

Except for depression or absence of light and accommodation reflexes and extraocular palsies in some instances, neurologic findings were essentially absent in these groups. In no instance was there any notable disturbance of bodily functions.

Roentgenograms disclosed changes in bony or soft tissue in all but three cases. Most commonly, there was evidence of osteomatous thickening of the wings of the sphenoid in the cases in which meningiomas arose in the region of the sphenoidal ridge. The sellar tumors eroded the optic foramen or caused formation of new bone in the region of the tuberculum sellae turcicae. The basofrontal group produced an area of increased density within the orbital space or a paranasal sinus in three cases.

Pathologic findings in primary intraorbital meningiomas

The primary intraorbital meningiomas were reddish, granular or nodular masses, varying in size from the small foraminal growths which measured a few millimeters in all diameters to a meningioma of the sheath which was twice the size of the eyeball. In this last case, proptosis of 17 mm. was present. Although the neoplasms often appeared encapsulated and usually presented well-defined boundaries, others had infiltrative tendencies. The extraocular muscles and the motor and sensory nerves within the orbit were engulfed by the expanding lesion in some cases (fig. 4). Total removal of such tumors results in loss of the function performed by the entrapped structures.

Four of the primary intraorbital meningiomas were of the meningotheliomatous type, 11 were psammomatous, and two were of the less common fibroblastic type. All of the foraminal growths were psammomatous. Three of the sheath tumors were meningotheliomatous and six were psammomatous. Of the five so-called extradural meningiomas, one was meningotheliomatous, two were psammomatous, and two were fibroblastic.

In tumors of the meningotheliomatous type, the cells were arranged in a solid pattern forming a cytoplasmic blanket in which the cellular boundaries were distinguished with difficulty (fig. 5). The substance of the tumor occurred in lobules limited by minimal strips of interstitial fibrous tissue. The nuclei were generally large, round or oval, vesicular, and were rather uniformly dispersed. Higher magnification of tissue in the same case as Figure 5, however, disclosed some departure from this strictly uniform, monotonous pattern in that some of the nuclei were irregular, pyknotic, and hyperchromic. These changes are probably indicative of intracellular degenerative changes.

The special Perdrau and Mallory phosphotungstic acid stains disclosed an absence of intercellular reticulin and collagen fibers. The presence of an occasional mitotic figure suggested a low degree of malignant activity.

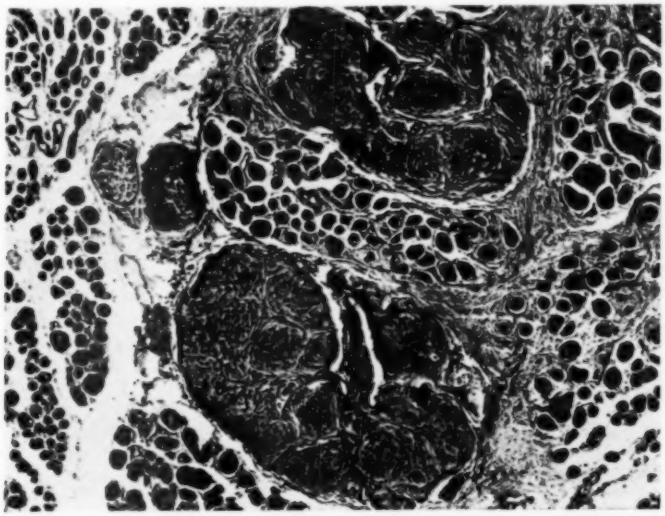

Fig. 4 (Craig and Gogela). Psammomatous meningioma. Small whorls of cells are clustered into lobules imbedded among striated muscles and nerves (hematoxylin and eosin, ×75).

The cells composing the meningotheliomatous type of tumor resembled the arachnoidal rest cells, or "cap" cells, which occurred in clusters within the optic nerve sheath (fig. 1).

The tendency toward "whorl" formation which distinguishes the psammomatous type is shown in Figure 4. The tumor cells were grouped into small circular lobules which were further subdivided into concentric whorls of meningotheliomatous cells. It is this characteristic whorling which serves as the important distinguishing criterion in identifying the two most common types of

meningiomas. The cell type is identical in the two. However, the cells forming the peripheral layer or two of the psammomas assume an attenuated appearance.

Figure 4 further serves to illustrate the invasive tendency of the meningioma, the two psammomatous lobules being firmly imbedded among bundles of striated muscle fibers and nerve fibers.

On examination under higher magnification some psammomas had been formed by the lamellar arrangement of cells about a small central capillary. More commonly, however, the cells were merely layered down on a cluster of central cells. The innermost cells often tended to degenerate and become granular (fig. 6). These bodies subsequently became hyalinized and infiltrated with calcium salts to form heavy, deeply staining, calcified masses (fig. 2).

The third histologic type of meningioma recognized in this series falls into the group designated by Bailey and Bucy[21] as "fibroblastic." While retaining some of the general characteristics of the two preceding types of meningiomas, the fibroblastic growths introduce certain new features. A definite, basic tendency toward whorling, distinctive of the psammomatous meningioma, may be recognized in Figure 7, which is from 1 of the 2 fibroblastic meningiomas encountered within the orbit. Numerous irregular spaces lend a suggestion of looseness to the tissue.

Examination of the detailed structure of the tissue disclosed some marked departures from the more regular, compact arrangement of tumor cells seen in the preceding growths. The cells were irregular and lacking in definite boundaries and the cytoplasm appeared to trail off into light, eosinophilic, interstitial material of a homogeneous or finely fibrillar make-up. The nuclei tended to be vesicular and irregularly oval in shape. The numerous vascular spaces usually appeared well formed and were lined with endothelial cells. An occasional mitotic figure was recognized.

Special preparations of this specimen dis-

Fig. 5 (Craig and Gogela). Meningotheliomatous meningioma. Cells are more or less uniform and are evenly dispersed. Collagen and reticulin fibers accompany blood vessels only (hematoxylin and eosin, ×75).

closed the presence of intercellular fibers. Silver stains brought to light delicate fibrils of reticulin interspersed among the cells and heavier strands of reticulin accompanying the larger vessels in their course. Moderate amounts of lightly staining, eosinophilic, intercellular wisps of collagenous material were demonstrable with Mallory's staining.

In this particular case, the tumor recurred and a subtotal exenteration of the orbit was performed nine years after initial removal.

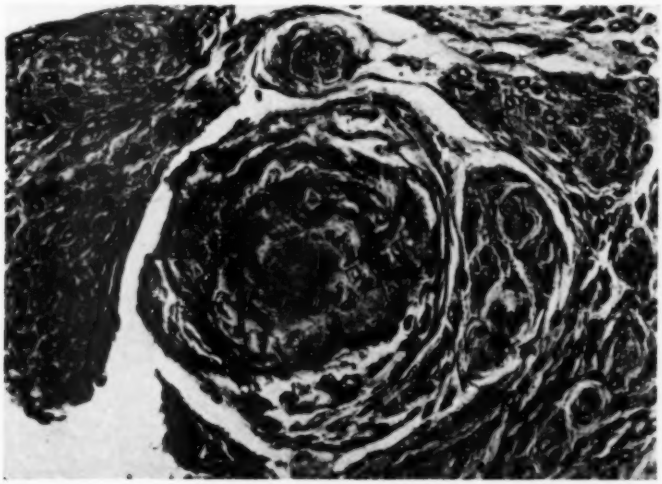

Fig. 6 (Craig and Gogela). Small, granular degenerating psammoma. Nuclear remnants are discernible (hematoxylin and eosin, ×350).

Surgical treatment

Although Scarpa removed an orbital growth which arose from the external sheath of the optic nerve without injury to the function of the eye as early as 1816, Byers's extensive list of more than 100 intraorbital tumors of various types disclosed that, in about 70 percent of the cases, extirpation of the eyeball and the tumor was performed.

Knapp,[22] in 1874, urged conservatism in the treatment of intraorbital neoplasms, and is generally considered as having introduced the less radical procedures. He made an opening through the conjunctiva and into Tenon's capsule between the rectus superior and the rectus internus. After he felt the tumor with his finger, he pried it out with a pair of scissors. Lagrange[23] modified the procedure by introducing external canthotomy.

In an effort to obtain more adequate exposure in approaching deep-lying, lateral, intraorbital tumors, Krönlein,[24] in 1888, devised an osteoplastic resection of the outer orbital wall extending down to the inferior orbital fissure. This procedure was later recognized to have definite limitations.

On anatomic examination of the orbit and its contents, McCotter and Fralick,[25] in 1943, pointed out that there are four anterior anatomic approaches to the removal of orbital tumors: (1) Resection of the temporal wall; (2) the external ethmoid approach nasally; (3) the brow incision for tumors located above the globe; and (4) the incision through the conjunctival fornix.

They concluded that only relatively small masses can be removed when these approaches are used.

Clinically, it had been recognized that the inaccessibility of intraorbital tumors and the inadequate approaches for their removal had long hampered satisfactory treatment of these growths. Although the tumors of the anterior part of the orbit could be removed readily by one of the "ophthalmic" procedures, those in a "retrobulbar" location also that of cerebrospinal fluid leak and consequent meningitis which served to deter the ophthalmic surgeon.

The inadequacy of the various available procedures was recognized at the time of Byers's survey in 1901 when, in commenting upon the prognosis of intraorbital tumors, he stated, "The danger is not from recurrence in the strict sense of the term, but from the continued development of the intracranial portion of the tumor which it is

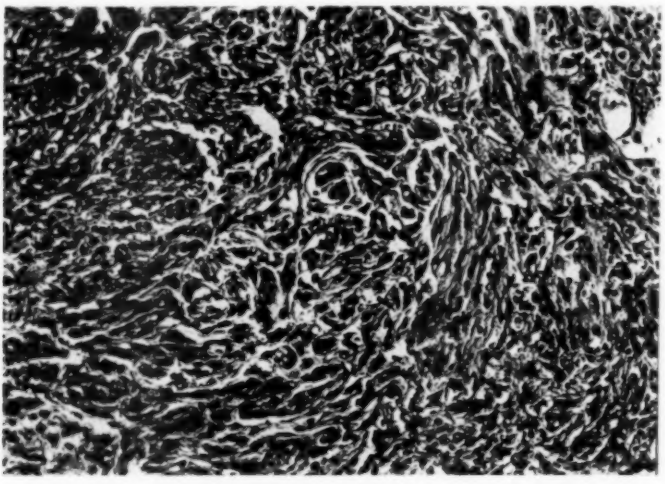

Fig. 7 (Craig and Gogela). Fibroblastic meningioma. A superficial tendency toward whorl formation is evident. Numerous small vascular spaces are present (hematoxylin and eosin, ×165).

had to be extirpated by touch which was an uncertain procedure.

Necessarily, many of the retrobulbar growths were removed incompletely and intracranial extensions were missed and allowed to expand within the cranium. Often, the exact nature and extent of the lesion were not recognized. Functioning eyeballs were sacrificed in an attempt at complete extirpation of tumors which could have been removed completely with preservation of sight if surgical exposure had been adequate. However, it was not only this risk of incompleteness and possible early recurrence, but impossible to remove at the time of operation."

Accordingly, with the pioneer work of Cushing and associate[8] and Dandy[15] in the use of the intracranial approach to the orbit, interest in the best methods of treatment of intraorbital growth received a stimulus. Simple modifications of standard surgical approaches afforded the neurosurgeon the advantages which would correct some of the ills which stopped the ophthalmic surgeon in his attack on these growths.

As Cushing and Eisenhardt so aptly put it, "The instincts and training of the neuro-

surgeon incline him at the outset to get to windward of the lesion with which he is to deal." On removal of a tumor via the intracranial route, Adson and Benedict[26] remarked that the procedure "suggests many possibilities for the transcranial approach optic-nerve sheath by the transtemporal route.

This mode of attack first suggested itself to Dandy[15] in 1918 when he sought to correct an exophthalmos due to an osteoma in a woman, aged 28 years. He resected a bony

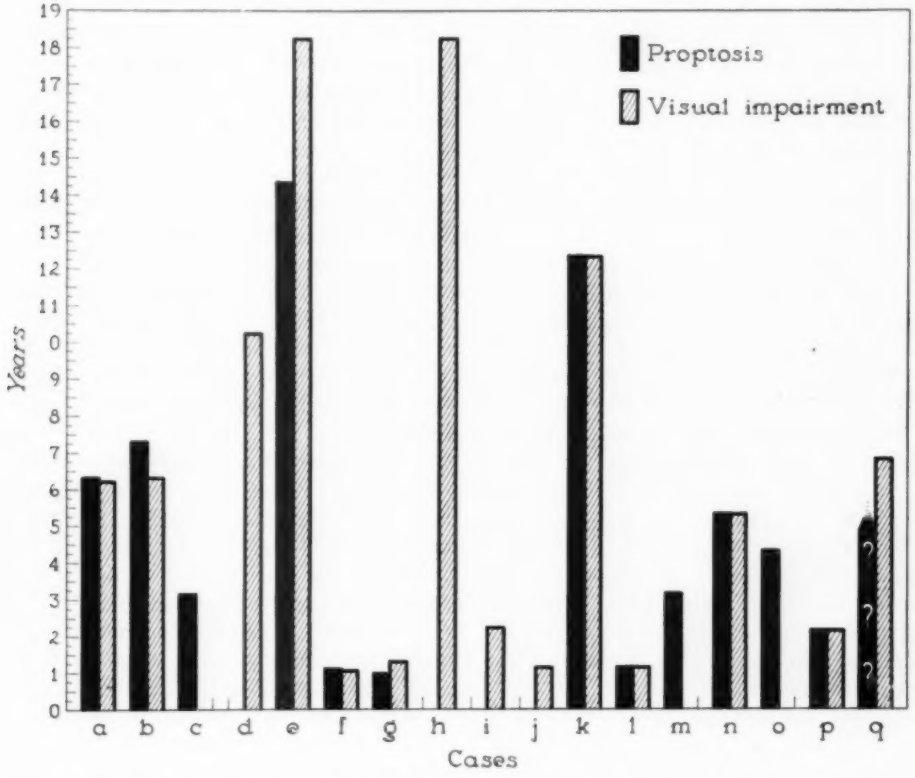

Fig. 8 (Craig and Gogela). Relative duration of proptosis and visual impairment in 17 cases of primary intraorbital meningioma. The case letters correspond with those in Figure 2.

to vascular and neoplastic lesions situated in the retrobulbar space of the orbit."

Dandy[27] employed the intracranial approach in removal of a combined intracranial and intraorbital growth for the first time in 1921; the particular case was one of bilateral meningioma of the optic sheaths. A short time later, Cushing and associate[8] exposed and removed a meningioma of the growth extending around the optic foramen, and, since the roof of the orbit appeared normal, he did not consider seriously its removal because, among other reasons, "of the deformity which would result by the gravity of the unsupported brain."

The original operative case of Dandy's[15] was that of a girl, aged 13 years, who had had bilateral, progressive decrease of vision for

six years. At the time of operation, the patient was almost completely blind. Exploration disclosed firm, collarlike growths enveloping both optic nerves and extending into the foramina. The visible intracranial portion of the larger mass was resected and the operation was terminated. At a second stage operation a short time later, the posterior half of the orbital roof and the dorsum of the optic foramen were chiseled away and the tumor was traced to the globe and removed subtotally. Dandy[27] emphasized strongly the need for a simultaneous approach to the cranial and orbital cavities when such tumors were considered to be present.

The case in which Cushing and associate removed an intraorbital meningioma was that of a woman, aged 39 years, who had had progressive protrusion of the eyeball with blindness for eight years. Failing to find any evidence of intracranial tumor on lateral osteoplastic exploration, he next attacked the orbit, chipping away the orbital surface of the sphenoid. He resected and removed the optic nerve along with the tumor. Cushing and associate, in commenting on this approach, remarked that the amount of "space for maneuver" which is afforded is "greatly restricted." Hence, his operative approach must be branded as less than satisfactory.

Despite the fact that Durante,[28] as early as 1887, used the frontal intracranial approach in a case of unilateral exophthalmos probably of meningeal origin, and despite the recommendations of Dandy[27] and Cushing and associate,[8] as to the type of surgical procedure best suited to these tumors, surgeons appeared to have been influenced only a little during the years which immediately followed.

Naffziger's[29] extensive experience with transfrontal decompression of the orbit for progressive exophthalmos has further served to illustrate and confirm the satisfactory nature of the intracranial route of approach to retrobulbar tumors.

Most surgeons,[6, 16, 19, 30-32] however, continued to employ the anterior approach into the orbit or the Krönlein osteoplastic flap. Elschnig,[33] in 1927, even recommended resection of the frontal lobe of the brain through the anterior orbital approach if the new growth encroached on the brain. Thompson,[34] in 1935, in presenting an intraorbital meningioma which he removed along with the globe through a Krönlein flap, felt that this approach was indicated for "intraorbital tumors" and the "Dandy operation" was indicated for the "prechiasmal type of tumor." He apparently drew a sharp distinction between the two.

Stallard,[35] in 1935, remarked that the operation of choice for the removal of the intraorbital "endothelioma" seems to be "partial or total exenteration of the orbit," depending on the size and extent of the neoplasm.

Shortly after Adson and Benedict, in 1934, reported the removal of a hemangio-endothelioma of the orbit through a transcranial approach, Love,[36] in 1935, published an account of the same procedure for the removal of an intraorbital meningioma.

The technique employed in the transcranial approach to tumors situated within the posterior portion of the orbit is essentially similar to that used most generally by neurosurgeons in the removal of tumors involving the pituitary gland. The procedure was described in detail by Love and Benedict[37] in 1945.

The scalp is dissected free from the underlying temporal muscles through a curved incision extending upward and forward from the ear. On elevation of the bone flap, the dura is stripped from the orbital roof (or the floor of the anterior fossa). The dorsum of the orbit is then perforated and contents carefully explored. If the tumor mass should be found to expand intracranially, the meninges may be incised along their attachment

at the sphenoidal ridge and the optic foramen may be approached from the intracranial side.

General anesthesia with open drop ether over the end of a Magill intratracheal tube is generally employed.

The transcranial approach to primary intraorbital meningiomas was used in 11 of our 17 cases. The tumors were removed through a brow or anterior incision three times and through the approach afforded by the Krönlein technique once. In two cases, subtotal exenteration was considered advisable. Since its introduction, the transcranial operation was used to the exclusion of the others in all but two cases.

No deaths resulted from any of the operative procedures, nor were there any serious postoperative complications to contraindicate the intracranial operation in favor of the less extensive procedures. The results of operation measured in terms of improved visual function were dependent largely on the location of the lesion and the preoperative duration of symptoms. Little return of vision was expected and obtained in those cases in which atrophy of the optic nerve was present to any degree.

Proptosis was definitely reduced in four cases treated by the transcranial operation and in the one case in which the Krönlein procedure was employed.

The tumor recurred in two cases, in one of which the tumor was of the rapidly growing fibroblastic type.

Comment

In order that reports of free-lying, unattached, primary intraorbital meningiomas may not be discredited, some source for these tumors must be postulated. In some instances, the tumor mass may lie between an orbital roof which is apparently intact and the extraocular muscles. It may be suggested that these growths arise from free strands of meningeal tissue invading the orbital cavity through the orbital fissures or that the intraorbital periosteum possibly serves to give rise to these meningiomas of unexplained origin.

Another explanation is that these "extradural" meningiomas may have had an arachnoidal attachment which subsequently disappeared during the process of growth.

Within the cranial cavity, the optic nerve is first enveloped only by the pia mater, but soon gains a covering of arachnoid. On reaching the optic foramen, the nerve acquires the third or dural layer and continues with its triple meningeal sheathing as it traverses the orbital chamber to penetrate the globe.

The closely adherent periosteal and meningeal layers of the intracranial dura mater separate into the periosteum of the orbit (or the periorbita) and the outer meningeal layer of the optic sheath. This periosteum is continuous with that of adjacent bones through every orbital opening.[27, 28] At the superior orbital fissure, it continues as the external layer of the dura. The potential subdural and the subarachnoid spaces formed by the meningeal coverings of the optic nerve are continuous with the corresponding intracranial spaces.

Anatomic descriptions fail to state whether any of the coverings of the nerves to the extraocular muscles are still present after these nerves have entered the orbital cavity. The ophthalmic artery and the ophthalmic veins are apparently devoid of meningeal vestments.

Examination of serial sections of these anatomic structures in this study disclosed that meningeal tissue does not accompany these nerves and vessels into the orbit. Nor were any arachnoidal cell clusters found to lie imbedded within the normal retrobulbar intraorbital tissues. Yet, 3 of the 5 extradural tumors were of the meningothelioma-tous or psammomatous type, tumors composed of a definite cell type arising only

from a similar preëxisting cell type.

Since no pathologic changes were encountered in the intracranial dura over the orbit at the time of operation, some other source must be postulated. The periorbita is composed of fibrous tissue and, therefore, cannot give rise to the meningotheliomatous or psammomatous tumors. It is suggested, therefore, that these extradural tumors may possibly have originated as arachnoid tufts which had grown into and through the dural layer of the optic sheath and had come to lie completely outside the dura.

Elsberg,[39] in 1933, and Kernohan,[40] in 1941, among others, have observed the presence of such extradural tumors in the region of the spinal cord, and the latter has offered just such an explanation for the presence of these growths in this region.

The presence of the foraminal meningiomas and of the meningiomas attached to the optic-nerve sheath may be explained adequately by the clusters or "caps" of arachnoidal cells occurring so abundantly along the intraorbital course of the optic nerve as suggested by previous investigators. In all probability, the cufflike growths arising within the optic foramen are but "sheath" meningiomas situated within a specific location. However, why this special predilection should exist and why these growths should demonstrate a tendency toward bilaterality is difficult to explain.

Microscopic examination of normal optic nerves and their sheaths did not disclose the clumping of arachnoid cells to be any more frequent or more exaggerated within the optic foramina than anywhere else along the intraorbital course of the optic nerve. Yet, 2 of the 3 foraminal tumors included in this series were bilateral, one of the growths appearing fully 16 years after its mate. Similarly, in Dandy's[15] single case of "cufflike" meningiomas the tumors were bilateral.

Reports of the occurrence of primary intraorbital meningiomas in children[6, 9, 30, 41] suggest that when these tumors occur, they do so in young persons. Hudson[42] stated that 50 percent of intraorbital meningiomas occur during the first two decades of life. Study of the 17 cases in our series, however, disclosed that the lesions appeared at much the same age as do meningiomas elsewhere within the cranium. The patients who had primary intraorbital growths came to operation at an average age of 41 years and those who had primary intracranial lesions which invaded the orbit secondarily were an average age of 43.5 years at the time of operation.

Analysis of the presenting findings (proptosis and loss of vision) failed to support the contention that the relative duration of the two diagnostic criteria may serve as a guide in differentiating these tumors from other intraorbital growths preoperatively. Investigators[32, 43] have offered precedence of exophthalmos over visual failure as a point of diagnosis in distinguishing intraorbital meningiomas from gliomas of the optic nerve. However, study of Figure 8 obliges us to conclude that such observations are unreliable criteria. Whether proptosis is to be the initial complaint, or whether the onset of visual failure will be noted first, appears to depend on the intraorbital location of the meningioma.

Although roentgen studies of the head and orbit are valuable adjuncts in the differential diagnosis of intraorbital lesions, they are probably more of negative rather than positive value in identifying primary intraorbital meningiomas. The fact that roentgenologic findings were negative in 65 percent of the primary tumors in this series is contrary to the contention that positive roentgenologic findings are suggestive of the presence of a primary intraorbital tumor. Moreover, when changes were present, they were not of a uniform nature specifically indicative of a particular lesion.

The secondary tumors, on the other hand, produced roentgenologic changes in more than 90 percent of this group. These figures

compel us to conclude that the presence of evidence of pathologic change about the orbit in the roentgenogram favors the presence of a secondary, or invading, intraorbital meningioma.

Summary and Conclusions

Seventeen cases of primary intraorbital meningioma and 35 cases of secondary intraorbital meningioma were studied in this series. The primary intraorbital meningiomas were subdivided into three groups: foraminal, sheath, and extradural.

The foraminal and the sheath meningiomas probably arose from clusters of arachnoid cells within the sheath of the optic nerve. No similar source was found to account for the extradural growths. It is suggested that they may develop from enlarging cell clusters protruding through the sheath of the optic nerve.

Intraorbital meningiomas are four times more common in women than in men and tend to occur during the middle years of life as do meningiomas located elsewhere.

The order in which proptosis and visual impairment appear does not serve as a reliable aid in distinguishing intraorbital meningiomas from other intraorbital lesions. Roentgenologic changes about the orbit are usually suggestive of an invading or secondary type of intraorbital meningioma.

The transcranial route of approach best meets any contingencies which may arise in the attack on these tumors.

Mayo Clinic.

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TRUE PSYCHOSENSORY DILATION AND DELAYED PSYCHOSENSORY DILATION OF THE PUPIL*

A PRELIMINARY REPORT

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It has long been known that the pupil will dilate in response to psychic and sensory stimuli. Fear, excitement, and rage all cause pupillodilation. Stimulation of sensory nerves similarly causes pupillodilation. The center and efferent pathway for these two different kinds of stimuli are considered identical and hence the phenomenon is known as the psychosensory reflex. This reflex has a relatively long latency period; between 0.292 and 0.46 seconds (Albrecht 0.292; Weiler, 0.36 to 0.44; Braunstein, 0.41 to 0.46).[1] The reflex consists of a quick dilation and contraction. The reaction is rapid and occurs bilaterally.

It is generally agreed that there is a cortical center for this reflex.[2] However, the efferent pathway has been the source of considerable controversy. It is more than of just theoretical importance since the reflex may be used in the practical differential diagnosis of anisocoria. The number of experiments performed in this connection has been legion, yet the conclusions drawn from them may be grouped into three main classes.

1. Dilation due to reflex inhibition of the oculomotor-nerve nucleus.

2. Dilation due to reflex peripheral sympathetic stimulation.

3. Dilation due to a combination of these two mechanisms.

Ury and Gellhorn[3] have concluded that reflex dilation occurs via inhibition of the third-nerve nucleus alone since third-nerve section abolished the reflex; whereas, it was still present after cervical sympathectomy. They also considered that the function was purely central, since stimulation of the legs of cats with unilateral sympathectomy resulted in dilation of both pupils.

Working independently, Anderson,[4] Tschirkowski,[5] and Nishimura[6] showed that, with the cortex intact and the sympathetic intact, cutting the third nerve did not abolish psychosensory dilation. Most investigators today are of the opinion that both factors come into play and that one may be present without the other.

It is probable that this reflex does not depend on the liberation of adrenalin from the adrenal medulla since it is an extremely rapid reaction. It must, therefore, be the result of pure antonomic nervous activity.

Cannon[7] has shown quite decisively that the adrenal medulla liberates its secretion in significant amounts only under conditions of stress. Adrenalin is called forth to resist threatened dangers, to perform work, to maintain homeostasis. Thus, the sympathetic nervous system is reinforced by the medullary secretion. For maximum efficiency in coping with emergency states the body requires two mechanisms:

(1) Nervous—via immediate sympathetic stimulation; (2) hormonal—via a delayed reaction which depends on the mobilization of the hormone from the adrenal medulla.

The center for the hormonal mechanism was placed by Cannon and Rapport[8] in the upper part of the floor of the fourth ventricle. This may not be the highest center since stimulation of the hypothalamus will cause a discharge of adrenalin.

It will be shown in the following experiments that much of the confusion regarding the psychosensory pupillary reflex may be

* This work was done under the auspices of the George Beldock Foundation. Read before the New York Society for Clinical Ophthalmology, February 2, 1948.

attributed directly to the failure to recognize that there may be two phases to this reaction. The first, immediate, rapid reaction is purely nervous, due to sympathetic stimulation and probably coincidental third-nerve inhibition. The second, delayed, slow reaction is purely hormonal and depends on the liberation of adrenalin by the adrenal medulla. The second phase will only occur if the stimulus is great; that is, if an emergency state is set up. With mild stimuli only the first part of the reaction will occur.

Experimental studies

Experiment 1

In this experiment only mild psychosensory stimuli were used; for example the crack of a gun.

Postganglionic cervical sympathectomy was performed on the right side of each of eight normal cats. Horner's syndrome was apparent within 10 seconds after the nerve section. Within 10 days, in all cats, the denervated iris (right) became hypersensitive to adrenalin. This is in accordance with Cannon's law of denervation.[9] For a more detailed explanation see a previous paper by me.[10] The present experiment was performed 2 to 3 months after the nerve sections. In no case was there any evidence of regeneration.

Each cat was placed in a cat box with the head protruding. Using Loewenstein's pupillographic technique,[11] 10 pictures per second were taken of both pupils under infrared illumination. After about three seconds, a gun was sounded. The reaction of both pupils to this psychosensory stimulus is shown in Figure 1. It is seen that the normal left pupil reacted well by dilating. The right pupil, however, showed a dilation which amounted to only one fifth the magnitude of the normal reaction.

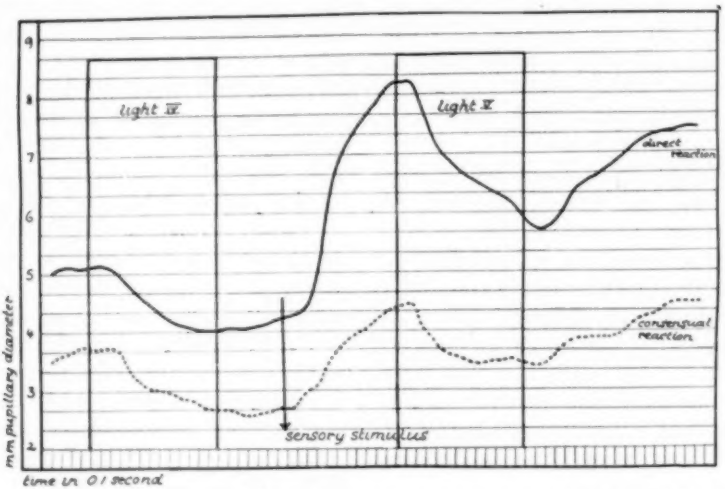

Fig. 1 (Jaffe). Dotted line represents the reaction of the sympathectomized right pupil. Continuous line represents the reaction of the normal left pupil. The pupils were stimulated by repeated light stimuli. Between the fourth and fifth stimuli a gun was sounded. The normal (left) pupil responded by dilating more than 4 mm. The sympathectomized (right) pupil dilated only about 1.5 mm. This demonstrates that peripheral sympathectomy largely, although not completely, abolishes psychosensory dilation.

The experiment was repeated using cats previously subjected to right preganglionic cervical sympathectomy. In all instances the results coincided with those above.

This is purely a nervous reaction and in-

volves a stimulation of the center in the cerebral cortex with subsequent peripheral sympathetic stimulation and third-nerve inhibition. In the normal eye, since the cortex, third nerve, and peripheral sympathetics are intact, the reaction is full. In the right eye we get a markedly diminished reaction because the peripheral sympathetic chain is not intact. There is no hormonal element in this reaction for, if adrenalin were liberated, the reaction in the denervated right iris would have far exceeded that in the normal iris because the effector cells of the denervated iris are hypersensitive to adrenalin (law of denervation). The small, residual reaction in the right pupil may be attributed to third-nerve inhibition.

Thus, it may be stated that mild psychosensory stimuli cause a dilation of the pupil and the integrity of this reaction is maintained by purely nervous factors—center in the cortex, peripheral sympathetic stimulation, and third-nerve inhibition; no discharge of adrenalin accompanies this reaction.

Experiment 2

In this experiment a strong emotional stimulus was used such as the excitement induced by ether anesthesia.

The eight postganglionic sympathectomized cats were used in this experiment. The cat was again placed in a cat box with the head protruding. Gauze moistened with ether was placed near the cat's nose. The animal immediately became excited. The normal left pupil dilated immediately. The right (denervated) pupil did not dilate until after 6 to 8 seconds of excitement. When it did dilate it dilated maximally and far exceeded the reaction on the normal side (figs. 2 and 3).

The same experiment was performed with the eight preganglionic sympathectomized cats. In all cases, there was an immediate dilation on the normal left side but a delayed and strong dilation on the operated right side. The reaction on the right side exceeded that on the left side but it was slower and of smaller amplitude than that observed with the postganglionic sympathectomized cats.

It is clear that we are concerned here with both phases of the psychosensory reflex referred to previously.

The immediate reaction on the normal side was purely nervous and occurred as a result of simultaneous peripheral sympathetic stimulation and third-nerve inhibition. The delayed reaction seen on the operated side was due to stimulation of the centers for adrenal secretion with subsequent liberation of the hormone and its action on the denervated iris.

Fig. 2 (Jaffe). Cat with postganglionic cervical sympathectomy on the right side. Photograph shows cat under normal conditions. Note miotic right pupil (Horner's syndrome). Left pupil is normal in size.

Fig. 3 (Jaffe). Same cat as in Figure 2 during ether excitement. Note that the sympathectomized right pupil responds by dilating more than the normal left pupil. This demonstrates the "law of denervation."

The delayed reaction is also seen with a preganglionic sympathectomized animal but it is not so marked since sensitization of denervated structures to circulating adrenalin

is twice as great in postganglionic sympathectomized animals.

That the reaction is due to sensitization is amply demonstrated by the fact that the normal pupil returns to its original size much sooner than the denervated pupil after the ether gauze is removed.[10] Thus, with a given increased adrenalin level, the denervated structure responds more markedly than the normal structure.

Experiment 3

This experiment eliminates the hormonal factor. In two of the postganglionic sympathectomized cats, bilateral adrenalectomies were performed. One week after the operation, the ether experiment was again performed. The cats became excited and the normal pupil dilated immediately. The denervated pupil, after 6 to 8 seconds, dilated only slightly (about two fifths of the usual reaction). See Figure 4.

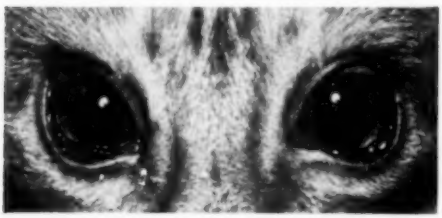

Fig. 4 (Jaffe). Same cat after right postganglionic cervical sympathectomy and bilateral adrenalectomy. The cat is shown during the excitement stage of ether anesthesia. Note that the right pupil dilates less than the normal left pupil and the right palpebral fissure is narrow. The right pupil doesn't show the "law of denervation" since the adrenal glands have been removed.

These animals could not, therefore, respond to the ether with both phases of the "fight or flight" reaction. The immediate nervous reaction was observed since the structures subserving this reflex were intact. The delayed, marked, hormonal reaction was practically absent since no adrenalin could be produced. The small, delayed dilation was probably due to some hepatic liberation of adrenalin.

Comment

These experiments show that the psychosensory pupillary reflex is a complex phenomenon consisting of two separate and distinct mechanisms. The true psychosensory reflex is a nervous reaction which has its center in the cerebral cortex. It exerts its effect by simultaneous peripheral sympathetic stimulation and third-nerve inhibition. It is an immediate reaction which has a latency period of 0.3 to 0.4 seconds. It occurs whether the stimulus is weak or strong.

The hormonal mechanism is a distinct mechanism and occurs only in response to a strong emotional or sensory stimulus. The reaction is best termed "delayed psychosensory pupillary reaction." Its center is in the floor of the fourth ventricle (perhaps in the hypothalamus). It exerts its effect by reflex stimulation of the adrenal medulla with subsequent liberation of adrenalin. The adrenalin thus formed passes to the iris by way of the blood stream and acts on the pupillodilator apparatus (fig. 5).

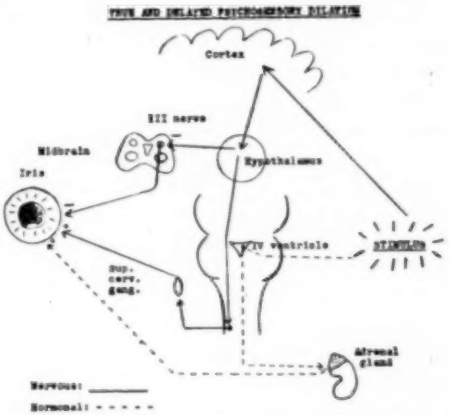

Fig. 5 (Jaffe). Diagrammatic representation of the pathways involved in true and delayed psychosensory dilation of the pupil. The continuous line represents the true or nervous reaction while the interrupted line represents the delayed or hormonal reaction.

Failure to recognize this delayed reaction in the past led to the erroneous interpretation of otherwise accurate observations.

As early as 1904, Anderson[4] noted that the normal pupil reacted to strong psychologic stimuli with an initial, rapid, and short dilation followed by a secondary dilation which developed and subsided more slowly and gradually. He attributed the initial reaction (the true psychosensory reflex) to stimulation of the sympathetic and the secondary dilation (delayed psychosensory reaction) to inhibition of the parasympathetic.

The latter view is untenable since reflex inhibition of the third nerve is a rapid reaction which proceeds from the cortex to the hypothalamus and then, by way of the inhibitory pathway, from the hypothalamus to the midbrain, and courses to the third-nerve nucleus which it inhibits. The distance traversed is shorter than that required for peripheral sympathetic stimulation. From the experiments herein reported it is evident that bilateral adrenalectomy would have eliminated the delayed, slow reaction. Consequently it could not have been due to third-nerve inhibition.

Ury and Gellhorn[3] more recently attributed reflex or emotional dilation of the pupil solely to inhibition of the third nerve since cutting the third nerve eliminates this. In Experiment 1, it was shown that when the cervical sympathetic chain is cut four fifths of the true psychosensory dilation is lost. Thus, the role of the sympathetic cannot be denied.

There is a further serious objection to this work. Cutting the third nerve gives a dilated pupil. Most workers believe this to be a maximally dilated pupil (problem unsettled). It cannot be expected that an emotional stimulus should further dilate such a pupil. They argue that instillation of pilocarpine contracts the pupil and still an emotional stimulus does not cause a dilation. However, it is well known that pilocarpine renders the pupil unresponsive to most stimuli (for example, reflex to light). Moreover, according to Walsh,[12] cutting the third nerve does not abolish psychosensory dilation.

Ury and Gellhorn further stated that the reaction must be a central one because stimulation of the legs of cats with unilateral cervical sympathectomy caused dilation of both pupils. However, it is probable that the dilation on the sympathectomized side was due to the delayed psychosensory reaction, since muscle contractions caused by stimulation give rise to adrenalin liberation with delayed stimulation of the sympathectomized iris. In this case, both pupils dilate but the pupil on the normal side dilates first.

Many more experiments have been performed and similar conclusions reached, but in all cases the same objections may be raised. Consequently no more instances need be cited. On the other hand, there has been much work done by others which firmly corroborates the results of the present experiments.

Byrne[13] showed that, after cervical cord transection, sciatic stimulation no longer evokes a primary reflex dilation but only a delayed form which usually occurs in 4 to 8 seconds after the onset of stimulation. The delayed dilation only occurred if the sciatic stimulation caused muscular contractions since the latter is associated with the liberation of adrenalin. If no muscle contractions occurred, no dilation occurred. Although Byrne used purely sensory stimuli his results have the same significance as those of this paper using psychosensory stimuli.

The work of Cannon[14] further shows that the reaction which depends on adrenalin liberation requires several seconds to begin. He used the denervated heart as an indicator of adrenalin liberation. Fright, rage, pain, asphyxia, and anesthesia caused, within 10 seconds, an increase in heart rate of 20 to 40 beats per minute.

Summary

Much of the controversy over the psychosensory pupillary dilation is due to the failure to recognize that this reaction is complex and involves two separate and distinct mechanisms.

The first phase is purely nervous and involves stimulation of the cerebral cortex with subsequent peripheral sympathetic stimulation and third-nerve inhibition. It is a rapid reaction, with a latency period of 0.292 to 0.46 seconds according to three different observers. It subsides rapidly. It does not involve medullary secretion of adrenalin. It occurs with both weak and strong psychologic or sensory stimuli. This may be called the true psychosensory dilation.

The second phase is purely hormonal. It is a delayed reaction. It subsides gradually. It involves stimulation of the center in the floor of the fourth ventricle or in the hypothalamus with subsequent release of adrenalin by the adrenal medulla. It occurs only in response to strong psychologic or sensory stimuli. This may be termed the "delayed psychosensory dilation of the pupil."

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Indebtedness is expressed to Dr. Otto Loewenstein whose pioneer work in pupillography stimulated the performance of these experiments.

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EXPERIMENTAL STUDIES ON SYMPATHETIC OPHTHALMIA*

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I. INTRODUCTION

This whole study is based on the allergy theory of sympathetic ophthalmia. The supporters of this theory hold that sympathetic ophthalmia is caused by an allergy to uveal pigment, melanin. De Schweinitz[1] points out that Bail and Heim gave the suggestion of the allergy theory to Kümmel and Elschnig and that Elschnig[2] went on to develop it in 1910-1911. Woods[3] has been the great champion of this theory in the United States. Despite a vast amount of work, this theory has yet to be established as fact. However, there are many observations which make the hypothesis sound most plausible. They are:

1. The time interval between the injury and the onset of the disease falls within the sensitization period as found in other immunologic experiments.

2. The histopathologic picture of sympathetic ophthalmia points strongly to an allergic basis for the disease—an allergy to pigment, as has been stressed by Friedenwald.[4]

3. The antibody reactions favor this theory. Elschnig[2] has shown that uveal pigment is capable of acting as an antigen which would cause the production of complement-fixing antibodies.

4. The skin tests with uveal pigment as described by Woods[3] suggest an allergic etiology.

5. That allergy to pigment is a factor seems indicated by the not infrequent reports in cases of sympathetic ophthalmia of bleaching of the eyelashes, leukodermic patches of the eyelids, and deafness due to involvement of the pigment cells of the inner ear.

6. Friedenwald[4] has reported an interesting case in which the sympathetic affliction had burned itself out over a period of many years and the eye was examined histologically. The choroid was replaced by scar tissue within which not a granule of uveal pigment could be found.

7. If one can evaluate therapy of this disease, it has been reported that massive salicylate therapy gives favorable results. Salicylates have been shown to reduce antibody formation in experimental animals.

8. The presence of eosinophiles in large numbers in eyes suffering from sympathetic ophthalmia points to an allergic condition.

II. RECENT ADVANCES IN THE STUDY OF AUTOALLERGY

One drawback to the acceptance of the allergy theory of sympathetic ophthalmia has been the great reluctance with which many men will accept the idea that a person can become sensitized to his own normal bodily constituents. Many years ago, Ehrlich coined the term "horror autotoxicus" to cast disparaging light on the work being carried on with regard to autosensitivity. However, advances in recent years in this field have proven Ehrlich wrong and have shown that autoallergy is not only plausible but that it does actually occur. Just to mention a few of the recent startling experimental results to sensitivity to one's own tissues we have:

1. In 1945 Cavelti and Cavelti[5] produced the clinical and pathologic picture of glomerulonephritis in rats by sensitizing them to rat kidney with the aid of Group-A beta hemolytic streptococcus.

2. Burky,[6] in 1934, produced endophthalmitis phaco-anaphylactica in rabbits by sensitizing them by the use of beef-lens toxin.

3. Another outstanding advance in the field of autoallergy came in 1946 when Kabat, Wolf, and Bezer[7] produced acute dis-

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seminated encephalomyelitis in monkeys by sensitizing them to monkey brain emulsion with the aid of adjuvants.

4. There seems to be some clinical evi-

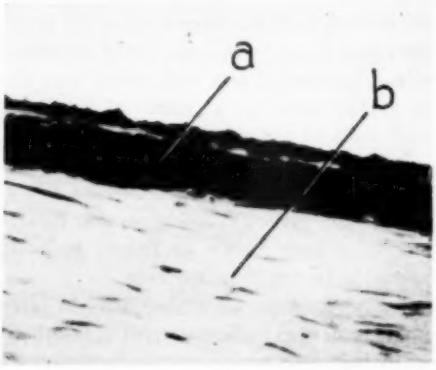

Fig. 1 (Collins). Section of human eye. (a) Nodule of lymphocytic infiltration in the choroid. (b) Sclera.

dence today that rheumatoid arthritis is the result of an individual's sensitivity to his own connective-tissue elements.

All of these observations indicate that autoallergy is an established fact and can no longer be held as a valid argument against the allergy theory of sympathetic ophthalmia.

III. Adjuvants

Many of the above-mentioned advances in the study of allergic conditions have come about as a result of the use of adjuvants. An adjuvant, as used in this sense, is defined as any material or materials which, when given in conjunction with an antigen, will intensify and prolong antibody production to this antigen. They will render a weak antigenic substance strongly so. Of all the numerous methods employed to increase antibody production the technique of Le Moignie and Pinoy,[8] (1916) with mineral oil emulsified in a lanolinlike substance, with or without the addition of killed tubercle bacilli, has been found to be the most effective.

The mechanism of action of adjuvants is a complex one which is not thoroughly understood. Most workers believe that adjuvants function by setting up a reactive tissue wall about the inoculum which localizes the antigenic material at the inoculation site and, through slow continuous absorption, produces hyperimmunization. They also feel that the large monocyte response called forth by the adjuvants increases the antibody formation (Rist,[9] Casals and Freund,[10] Freund, Casals and Genghof,[11] Friedenwald[12]).

IV. Pathology of sympathetic ophthalmia

The histopathologic picture of sympathetic ophthalmia has been adequately described numerous times by competent observers. Therefore, only a brief review will be given with examples for ready comparison and evaluation of experimental results to follow. Because many eyes suffering from sympathetic ophthalmia are removed late, a mistaken belief is that the histopathologic picture should always show the iris and choroid solid with lymphocytes, epithelioid cells, and some giant cells. However, the picture which one actually sees depends on the

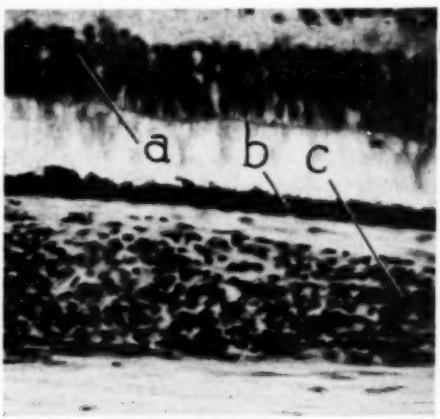

Fig. 2 (Collins). Section of human eye. (a) Retina. (b) Pigment epithelium with intact choriocapillaris below. (c) Nodule of infiltration in choroid, showing epithelioid cells in center of nodule.

age of the condition, and it apparently develops in stages:

1. Stage one is characterized by a focal infiltration of lymphocytes especially in the choroid and often around large veins. Figure 1 is a photomicrograph of a nodule in the choroid of an eye which was removed seven weeks after the original injury and immediately after the appearance of cells in the anterior chamber of the sympathizing eye. The nodule consists entirely of lymphocytes and there are only two such nodules in the whole choroid, as shown in the numerous sections prepared—the remainder being entirely normal.

2. Stage two is characterized by typical nodules in the choroid and iris of lymphocytes, epithelioid cells, and with or without giant cells. Figure 2 shows a nodule in the choroid of an eye removed because of sympathetic ophthalmia four months after a cataract extraction. The nodule consists of lymphocytes and epithelioid cells. The choriocapillaris is spared, and the choroid between the nodules is normal. The time interval in this case is approximately the same as that during which the experimental animals were followed and is thus interesting for comparison.

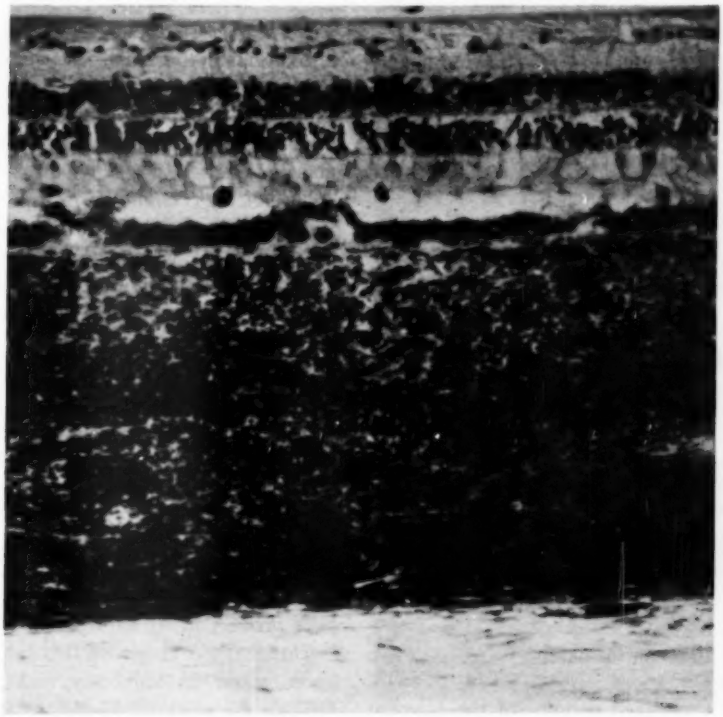

Fig. 3 (Collins). Section of human eye, showing tremendous thickening of choroid with lymphocytes and epithelioid cells.

3. Stage three shows the full-blown picture of the choroid uniformly infiltrated with lymphocytes and epithelioid cells and giant cells, especially the outer layers. Figure 3 illustrates this stage. This eye was removed because of sympathetic ophthalmia eight months after the original injury.

4. Stage four is the destructive phase in which the whole tissue is replaced by connective tissue.

No discussion of the pathology of sympathetic ophthalmia would be complete without mentioning the Dalén-Fuchs nodules. These are localized nodules of the pigment epithelium of the retina which were first described by Dalén[13] in 1904 and then by Fuchs[14] in 1905. They are formed by a localized proliferation of the pigment epithelium which has undergone autolysis and has been invaded by macrophages and epithelioid cells.

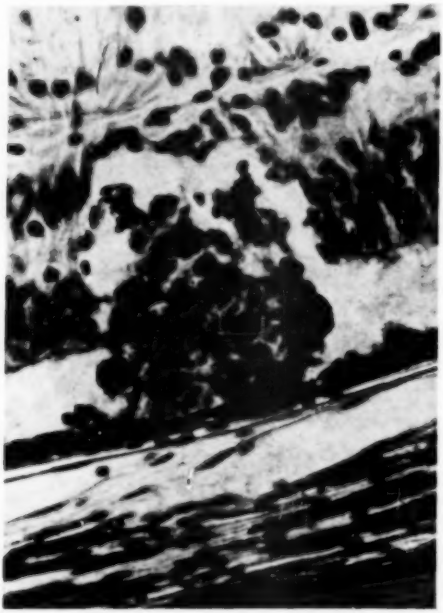

Fig. 4 (Collins). Dalén-Fuchs nodule in human eye.

The Dalén-Fuchs nodules are considered by some to be pathognomonic of sympathetic ophthalmia. Others claim that they are found in inflammatory conditions, particularly tuberculosis. However, Friedenwald[4] stresses that the alterations of the pigment epithelium seen in other conditions never show the evidence of autolysis and phagocytosis by epithelioid cells of the pigment granules as seen in sympathetic ophthalmia. Figure 4 shows a typical Dalén-Fuchs nodule from a human case of sympathetic ophthalmia.

V. Experimental work

1. The goal of this study was to produce in experimental animals a condition that simulated what is known as sympathetic ophthalmia in humans. This must be accomplished before the allergy theory can be established as fact.

2. Choice of animal. For this work we have chosen to use the guinea pig, because Zinsser[16] some years ago pointed out the similarity of the immune and anaphylactic reactions in guinea pigs and human beings. We learned from experience that white pigs with pigmented eyes or predominantly white pigs gave the best results in our work.

3. Antigen. In this work, macerated whole uvea was used as the antigen. It is true that the pigment of this tissue is believed to be the antigenic factor. Nonetheless, with our present meager knowledge regarding the chemistry and properties of melanin, it was felt that it would be impossible to obtain the pure product in its natural state.

Chemists working with this substance disagree about its solubility and properties. Despite the work of Elschnig,[2] von Szily,[15] and Woods,[3] who report on the use of pure pigment, it was felt that this was still impossible.

Mason,[10] after a review of the many works on the chemistry of melanin, states, "One is led to the conclusion that only the most gentle methods of separation of the pigment from its naturally occurring concomitants can be expected to yield an unchanged product. The weight of evidence indicates that, in the majority of cases in which isolation of melanin has been reported, the compositions found represent those of altered natural pigment. Since the recent study of Herrmann and Boss it has become evident

that the melanin granule is a highly complex aggregate not only of pigment, but also of at least three enzyme systems in a protein matrix. Should the pigment, which is apparently quinonoid, initially be bound to the granule by few or no primary valence bonds, it is likely on chemical grounds that destruction of the organization of the granule would result in rapid conjugation."

The pigment granule is intracellular, and it was felt that, with a limitless number of washings, one could never obtain pure pigment by mechanical means. Once chemical methods have been applied there is no way of knowing how the antigenicity of the melanin has been altered.

4. Procedures and results. In work on immunity it is known that young, healthy animals produce the highest titer of antibodies. Thus we used in all cases young, healthy guinea pigs.

SERIES ONE

Heterologous uveal tissue antigen. It is believed by many that uveal pigment is organ specific and not species specific, or only weakly so. Thus, in this series an attempt was made to sensitize guinea pigs to beef uvea (heterologous). Two animals were given intraperitoneal injections and four were given intramuscular injections of a mixture containing macerated whole beef uvea and adjuvants, which will be described later.

Three months after the last injection of this material the animals were killed and the eyes examined histologically. Of the six animals followed, one was positive (two eyes) and five were negative.

By positive is meant that the sections of the eyes showed good-sized areas of focal infiltration of lymphocytes and epithelioid cells in the choroid.

Figure 5 shows a nodule consisting of lymphocytes and epithelioid cells in the choroid of the left eye of the positive animal. Figure 6 shows a similar nodule in the right eye of the same animal. The choroids of both eyes were filled with numerous such nodules. Bruch's membrane was intact and the retina was normal throughout.

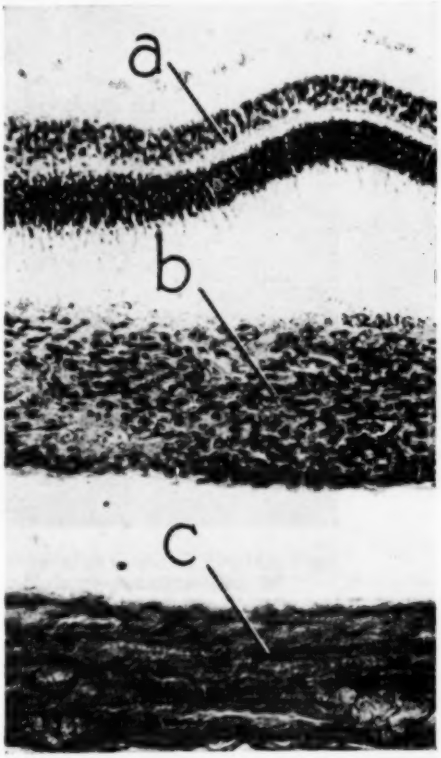

Fig. 5 (Collins). Section of left eye of guinea pig No. 292. (a) Retina. (b) Nodule of lymphocytic and epithelioid-cell infiltration in choroid. (c) Sclera.

SERIES TWO

Homologous uveal tissue antigen. In this series, an attempt was made to produce the picture of sympathetic ophthalmia in guinea pigs using guinea pig uvea as the antigen (homologous). The procedure was as follows:

A saline suspension of macerated guinea pig uveas was mixed with mineral oil, aquaphor, and heat-killed tubercle bacilli. Each

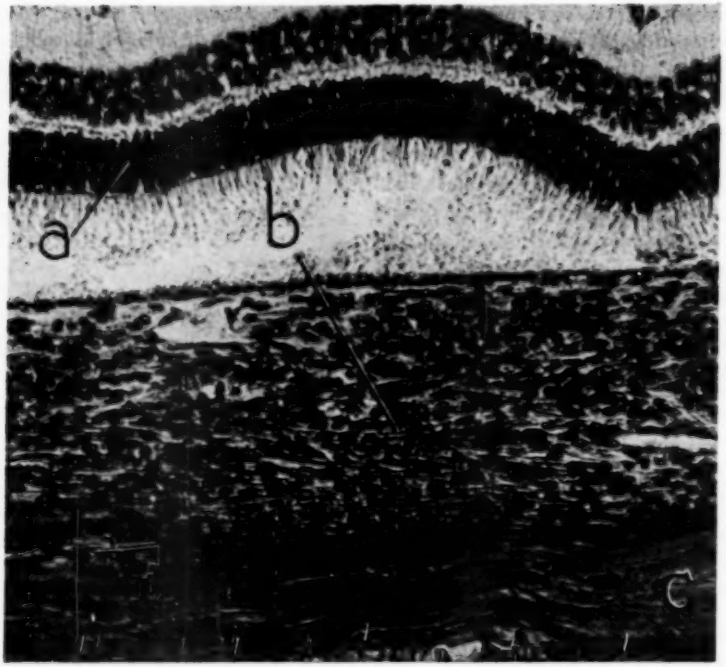

Fig. 6 (Collins). Section of right eye of guinea pig No. 292. (a) Retina. (b) Nodule of lymphocytic and epithelioid-cell infiltration in choroid. (c) Sclera.

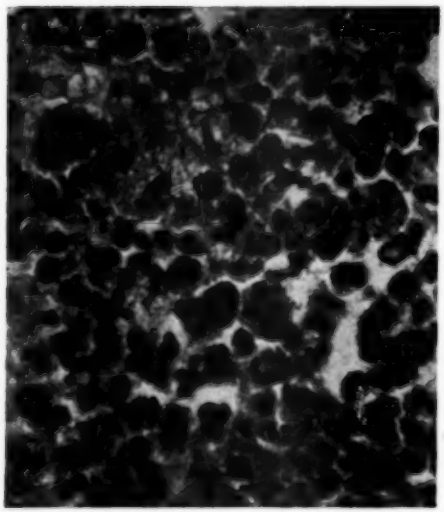

Fig. 7 (Collins). Biopsy of inoculation site.

injection was composed of 0.2 cc. paraffin oil, 0.1 cc. of aquaphor, heat-killed tubercle bacilli (0.5 mg. in the first, 0.85 mg. in the second, and 0.5 mg. in the third batch of antigen mixture), and 1.6 uveas per injection in the first mixture, 3.35 uveas in the second, and 0.7 uveas in the third.

This material was injected intramuscularly or intraperitoneally into 25 young, healthy guinea pigs. Each animal received 0.5 cc. of the above mixture in a leg muscle at weekly intervals for three doses. A fourth such injection was given at the end of five weeks. In a few, the fourth intramuscular injection was replaced by an intraperitoneal injection of the same amount. The animals were followed for from 3 to 6 months after their first injection.

Immediately before killing 12 of the animals, a sterile sample of blood was drawn

from the heart. Complement fixation tests run on these 12 sera showed no complement-fixing antibodies to guinea-pig uvea.

Because there is a virus theory of sympathetic ophthalmia, eight of these blood samples were studied for the presence of a virus. No virus was isolated by the routine methods of checking for these organisms. Likewise, because there is a bacterial theory of this condition, eight of the samples were cultured for the presence of bacteria and all of the specimens of blood were found to be sterile. An electrophoretic pattern was run on one serum and no increase of gamma globulin was demonstrated.

At the end of the chosen interval, that is, from 3 to 6 months, the 25 animals were weighed and killed. All 25 had gained much weight and appeared healthy. The eyes were removed immediately after death and fixed in Zenker's fixative and serial sections were made of all the eyes. Biopsies were taken of lung, liver, spleen, kidney, and inoculaiton site in all of the animals.

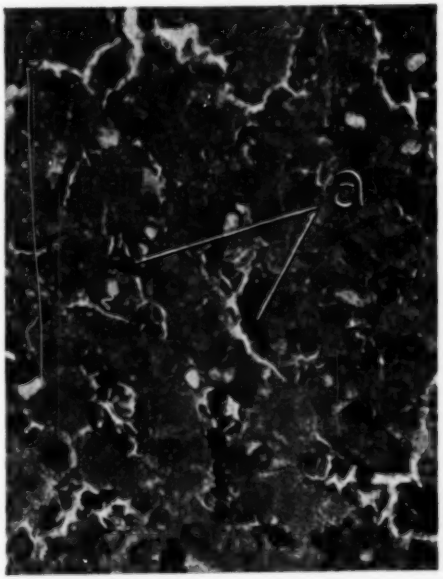

Fig. 8 (Collins). Biopsy of liver of treated guinea pig. (a) Kupffer cells filled with uveal pigment.

Figure 7 shows a biopsy of an inoculation site of one of the animals. It shows the great mononuclear response called forth by the mixture, and the phagocytosis of pigment

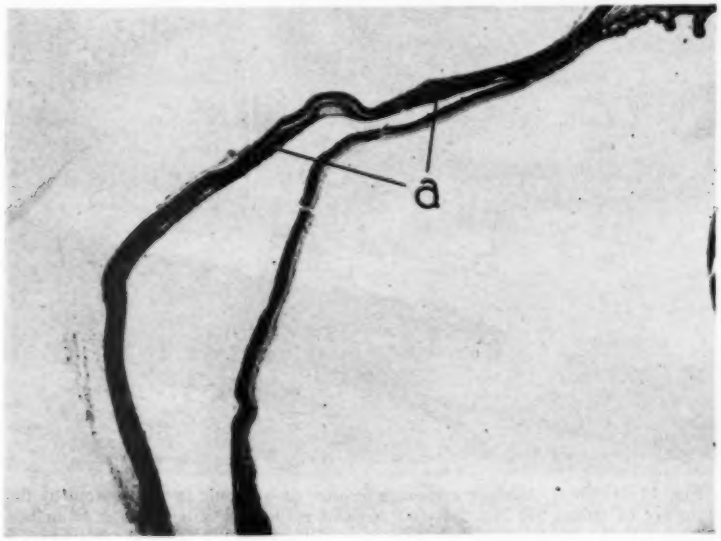

Fig. 9 (Collins). Low-power magnification of a section of left eye of guinea pig No. 253. (a) Nodules of infiltration in the choroid.

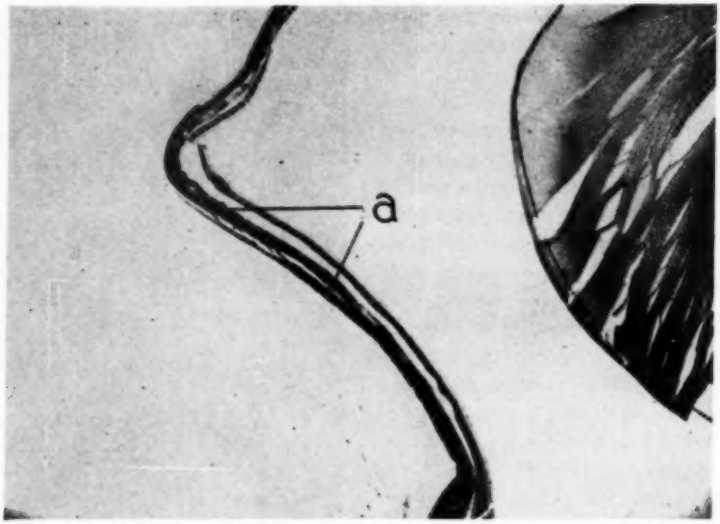

Fig. 10 (Collins). Low-power magnification of a section of the right eye of guinea pig No. 253. (a) Nodules of infiltration in the choroid.

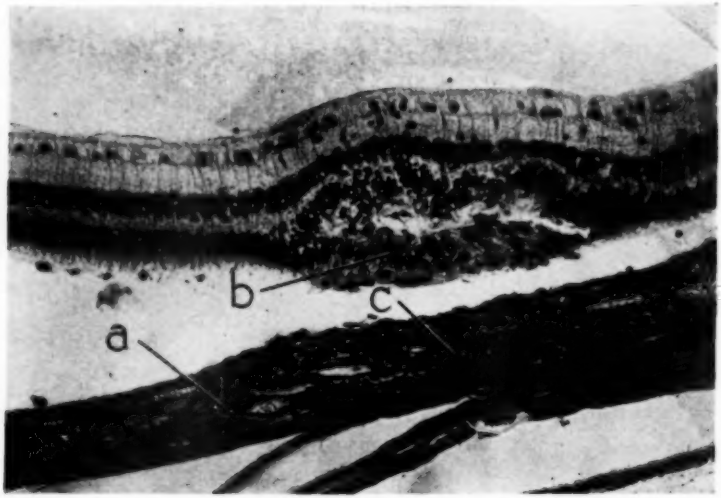

Fig. 11 (Collins). High-power magnification of a nodule in the choroid of the right eye of guinea pig No. 253. (a) Area of epithelioid cells in center of nodule in choroid. (b) Proliferation of pigment epithelium. (c) Area of lymphocytes in choroidal nodule.

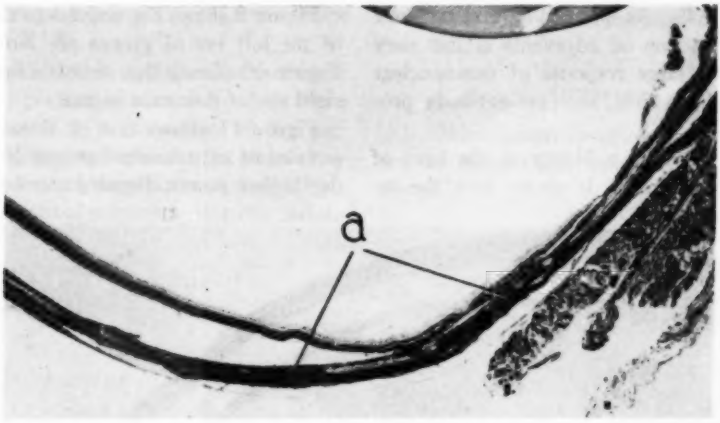

Fig. 12 (Collins). Low-power magnification of a section of left eye of guinea pig No. 133. (a) Nodules of lymphocytic and epithelioid-cell infiltration in choroid.

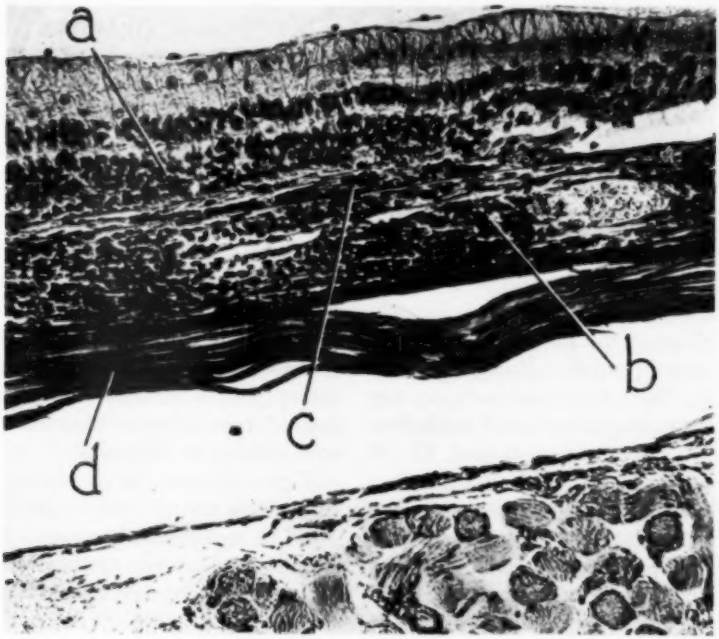

Fig. 13. (Collins). High-power magnification of a choroidal nodule in the left eye of guinea pig. No. 133. (a) Retina. (b) Nodule of lymphocytic and epithelioid-cell infiltration in the choroid. (c) Proliferation of pigment epithelium. (d) Sclera.

by these cells. As pointed out above, one theory of action of adjuvants is that they call forth a large response of mononuclear cells which, in turn, increase antibody production.

Figure 8 shows a biopsy of the liver of one of the animals. It shows how the reticulo-endothelial system of the liver, the Kupffer cells, have phagocytosed the pigment. Biopsies of the lung and spleen also showed marked phagocytosis of pigment by this system. The reticulo-endothelial system is important in the formation of antibodies.

Of the 25 guinea pigs so treated, 12 (24 eyes) were positive, that is, showed large areas of focal infiltration of lymphocytes and epithelioid cells in the uvea and changes in the pigment epithelium resembling Dalén-Fuchs nodules. It is to be emphasized that the eyes of these experimental animals were never touched or traumatized in any fashion until they were removed for sectioning after the death of the animal.

Figure 9 shows the nodules in the choroid of the left eye of guinea pig No. 253, and Figure 10 shows the same findings in the right eye of this same animal.

Figure 11 shows one of these choroidal nodules of experimental animal No. 253 under higher power. Bruch's membrane is in-

Fig. 14 (Collins). Low-power magnification of a section of right eye of guinea pig No. 133. (a) Nodules of lymphocytic and epithelioid-cell infiltration in the choroid. (b) Dalén-Fuchs nodule.

tact and there has been a proliferation of the pigment epithelium of the retina and some loss of retinal substance over this nodule probably as a result of an autolytic process taking place in the nodule. Careful examination of these sections shows that there is no true invasion of the retina.

Figure 12 shows the nodules in the choroid of the left eye of another positive animal, No. 133, and Figure 13 shows a high power magnification of one of these nodules. The nodule is composed of lymphocytes and epithelioid cells, Bruch's membrane is intact, and the choriocapillaris is spared.

Since sympathetic ophthalmia is a bilateral condition, Figure 14 shows the nodules in

the choroid of the right eye of this same animal, No. 133.

Figure 15 shows a Dalén-Fuchs nodule from the right eye of animal No. 133. Here again one sees a proliferation of the pigment epithelium, epithelioid cells, and an evidence of an autolytic process as shown by a loss of the retinal substance over the nodule. Many of the eyes of the positive animals showed these nodules.

Series three

Controls. Nineteen guinea pigs were run as controls. Fourteen of these animals received four intramuscular injections at the same time intervals as was used in the treated animals, that is, 1, 2, 3, and 5 weeks.

Each injection, consisting of 0.5 cc., contained the same amount of adjuvant—aquaphor, mineral oil, and heat-killed tubercle bacilli (0.5 mg. per injection)—as was used in the test animals above.

In addition, each injection contained an amount of albino guinea-pig liver tissue equivalent in dry weight to the approximate dry weight of guinea pig uvea in each experimental animal injection. Albino guinea-pig liver was chosen as a neutral, noneye tissue which we could be certain contained no melanin.

Five of the 19 guinea pigs received the same series of intramuscular injections of adjuvant alone. Each injection contained the same amount of adjuvant—mineral oil, aquaphor, and heat-killed tubercle bacilli—as was used in the treated cases.

All of the control animals were followed for from 3½ to 5 months. At the end of the chosen time interval, the animals were killed and biopsies of the lung, liver, spleen, kidney, and site of injection were taken. The eyes were removed immediately after death and fixed in Zenker's fixative and serial sections were made of all the eyes.

Microscopic examination of every section showed all of the 19 control guinea pigs (38 eyes) to be negative, that is, there were no abnormal histologic findings in any of the eyes.

Summary

1. Observations favoring the allergy theory of sympathetic ophthalmia were presented.

Fig. 15 (Collins). High-power magnification of Dalén-Fuchs nodule in right eye of guinea pig No. 133.

2. The histopathologic picture of sympathetic ophthalmia was briefly reviewed.

3. Experimental work showing an attempt to sensitize guinea pigs to uveal tissue with the aid of adjuvants, mineral oil, aquaphor, and heat-killed tubercle bacilli was presented. One (two eyes) of six guinea pigs, using heterologous uveal tissue, beef uveas, plus the above adjuvants, showed focal areas of lymphocytes and epithelioid-cell infiltration in the choroid of both eyes.

Twelve (24 eyes) of 25 guinea pigs using homologous uveal tissue, guinea pig uveas, plus adjuvants showed similar lesions. Many showed Dalén-Fuchs nodules.

Nineteen control guinea pigs given adju-

vants plus albino-liver tissue, or adjuvants alone, showed no abnormal findings in the eyes.

630 West 168th Street (32).

The author wishes to express his appreciation to Dr. Ludwig von Sallmann for his many valuable suggestions; to Dr. Alson Braley and Mrs. R. Alexander for carrying out the virus studies; and to Miss P. Pfaff for preparing the microscopic sections.

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Discussion

Dr. Jonas S. Friedenwald (Baltimore): I think Dr. Collins' report is very impressive. I would like to have more detailed histologic pictures before I can make up my own mind as to whether the picture produced, and to what extent the picture produced, resembles that of sympathetic ophthalmia.

I should like to make one point in regard to whether or not melanin itself is the necessary antigen in an allergic theory of sympathetic ophthalmia. A number of years ago Dr. Robert Hare and I were studying the skin reactions of patients with sympathetic ophthalmia to various inocula, and comparing the reactions to those produced in the skin of these same patients by uveal pigment preparations.

We found that we could make an emulsion from the choroid of albino rabbits which, when injected intradermally into sensitive patients, elicited an epithelioid-cell and round-cell reaction quite analogous to that produced in the same patient by an emulsion of choroid from a pigmented rabbit, and consequently we concluded that the melanin itself was not the antigen, but perhaps the melanin granule contained a matrix which was the antigen.

Dr. Robert Day (Baltimore): Were there any changes in the anterior uvea or any clinical signs?

Dr. David G. Cogan (Boston): I would like to ask the essayist if he investigated other pigment-bearing structures; for example, in the choroidal plexus, and if there was any lymphocytic reaction anywhere else in the body. From the pictures, I would judge not.

Dr. Raymond C. Collins (New York): The question as to whether or not there were any changes in the anterior uvea: The iris was entirely free. Many of them showed mild infiltration of lymphocytes in the ciliary body.

As to whether there was a lymphocytic reaction elsewhere in the body, biopsies taken as outlined, of the lung, liver, spleen and kidney, showed no lymphocytic infiltration, merely this phagocytosis of pigment that you saw on the slides.

Dr. Cogan: Lymphocytic reaction in other pigmented-bearing structures? Did you investigate any other pigment-bearing areas?

Dr. Collins: No, we did not.

Dr. Cogan: That would be an interesting thing to do.

DETACHMENT OF THE ANTERIOR LAYERS OF THE IRIS (IRIDOSCHISIS)*

Report of a case‡

Jay G. Linn,† M.D., and Jay G. Linn, Jr., M.D.
Pittsburgh, Pennsylvania

A separation or detachment of the anterior layers of the iris is a very rare condition, first described by Schmitt[1] in 1922 and named iridoschisis (iris splitting) by Loewenstein and Foster[2] in 1945. It is an acquired condition of a degenerative nature and is characterized by a separation of the iris into two distinct layers. The anterior layer appears as a thin transparent stratum of iris tissue attached to the posterior layer centrally in the region of the sphincter and peripherally near the iris root. The main body of this layer is composed of radial fibers which, in places, undergo fragmentation. The loose ends float singly or brushlike in the aqueous. The posterior deeply pigmented layer of the iris is easily seen through this anterior layer even where no fragmentation has occurred.

Ten cases have previously been reported in the literature to which we are adding an eleventh. They are as shown in Table 1.

Case report

Clinical history. B. C. L., a 58-year-old white man, was first seen by one of us (J. G. L.) in May of 1938, at which time he complained of blurred vision of the right eye. The corrected vision at that time was: R.E., 20/100; L.E., 20/200. He had always had poor vision in the left eye and an operation was performed in 1912 to correct a left esotropia.

A diagnosis of chronic simple glaucoma of the right eye was made on the initial examination and a corneoscleral trephining operation was performed a few weeks later. Good filtration was obtained and the postoperative corrected vision was 20/50+3. The tension has remained normal or subnormal since the operation.

In October, 1946, a reduction of the vision of the right eye caused by a nuclear cataract was noted. Ophthalmoscopy at this time revealed a pallor of the disc and pigment deposits in the retina.

In February, 1948, an atrophy of the iris with detachment of the anterior layers was first noted. The lenticular opacity had progressed and the fundus could not be seen.

Past medical history. Our patient had an appendectomy performed in 1928 which was followed in four weeks by a right nephrectomy for a kidney stone. Postoperative culture from the kidney was positive for Mycobacterium tuberculosis. He has enjoyed good health since that time.

Present ocular findings. In October, 1948, visual acuity of the right eye was 4/200 and of the left eye, 20/200. The right eye was divergent about 10 degrees. Both pupils reacted normally to light.

Slitlamp examination. Right eye. There was beginning endothelial dystrophy of the cornea (cornea guttata). No keratic precipitates were present and the aqueous was clear.

The iris had a surgical coloboma at the 12-o'clock position from the corneoscleral trephination. The entire iris was atrophic. This atrophy was more advanced in the ciliary zone. In this area, between the

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* From the Department of Ophthalmology, University of Pittsburgh, School of Medicine. Presented at the meeting of the Pittsburgh Ophthalmological Society, October 25, 1948.

† Professor of ophthalmology.

‡ Since this case was reported at the meeting of the Pittsburgh Ophthalmological Society, Dr. Robert F. Rohm has kindly permitted us to see one of his patients with bilateral detachment of the anterior layers of the iris. She is a white woman, aged 82 years, with bilateral narrow-angle glaucoma and immature cataracts. There is no systemic disease.

TABLE 1

CASES OF IRIDOSCHISIS IN THE LITERATURE

Author and Year	Age and Sex	Associated Ocular Findings	Systemic and Other Factors
Schmitt[1] 1922	74 F.	Mature cataract	Neurodermatitis circumscripta chronica, asthma
Drapkin[3] 1923	74 F.	Cortical cataract	
Sander[4] 1925	78 M.	Immature cataract	
Vogt[5] 1926	70 F.	Chronic iridocyclitis	
Schoenberg[6] 1927	51 M	Chronic simple glaucoma	Traumatic history as a high diver
Imre[7] 1927	92 94		
Dollfus[8] 1927	F.	Cataract	Diabetes mellitus
Loewenstein and Foster[2] 1945	76 F.	Iritis, glaucoma, and nuclear cataract	Osteoarthritis
Loewenstein, Foster, and Sledge[9] 1948	46 M.	Secondary glaucoma	Blunt blow to globe
Linn and Linn	58 M.	Chronic simple glaucoma, nuclear cataract	Tuberculosis of kidney with stone formation

sphincter muscle and the base of the iris, there was a separation into two layers. This was more evident in the nasal half of the iris. The main body of the anterior layer consisted of radial fibers. Some of these fibers contained granules of uveal pigment. In the area between the 3- and the 6-o'clock positions there had been a rupture of these radial fibers. The free ends were floating in a brushlike manner in the aqueous. A depigmentation of the anterior layer had resulted in a translucency which enabled the slitbeam to pass through so that the deeply pigmented posterior layer could be easily observed. This translucency was reduced in the region of the sphincter which apparently was uninvolved because the pupil reacted promptly to light. Examination of the lens revealed a diffuse nuclear opacity.

Left eye. The cornea had a nebulous opacity involving the stroma of that portion just below the pupil. An endothelial dystrophy in the same stage as that of the right eye was present.

There was beginning atrophy of the iris with some absorption of pigment of the anterior layers. Only in some areas had this depigmentation progressed so that the posterior layers could be seen through the anterior. No separation of the layers was evident. No cataract formation was evident in the lens.

Gonioscopy. Examination of the angle of the anterior chamber with the Allen prism revealed complete occlusion of the angle of the right eye by peripheral anterior synechia.

The angle of the left eye was open only in a small area of the nasal portion. No pigment could be seen in this area.

COMMENT

Histologic studies of the iris have been reported by Loewenstein, Foster, and Sledge[2, 9] which confirm the biomicroscopic findings. They found general atrophy of the iris

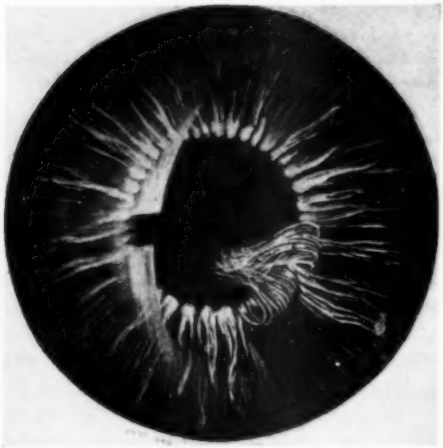

Fig. 1 (Linn and Linn). Appearance of the detachment of the anterior layers of the iris in the case herein reported.

tissue. The anterior layer consisted in some places of "thin floating membranes" and in others of "fragile grayish tissue like the finest lace." The free floating radial fibers were found to contain a blood vessel with a thickened endothelium. The blood vessel was filled with erythrocytes. The sphincter muscle was normal and the dilator fibers were hypertrophied. In their second case there was some evidence of phagocytosis of pigment.

An analysis of the reported cases reveals no specific cause for this peculiar form of iris atrophy. Senility, glaucoma, trauma, iritis, and diabetes have been suggested by individual authors. Apparently, any of these may be a factor which acts on the more delicate spongy tissue of the iris. The atrophy of the more dense and better differentiated tissues of the iris may follow at a later stage.

In no case has any synechia of the freely floating fibers to the cornea been recorded. No hyphema has resulted from rupture of these fibers.

Dollfus[8] performed an iridectomy on his patient which he followed in one month with a lens extraction. There was no complication of either procedure. We plan to extract the lens of our patient at a later date.

Our case is significant only in that the ruptured radial fibers of the anterior iris layer are possibly more prominent and the artist has been able to demonstrate them (fig. 1) better than in the previously reported cases.

Summary

A case of detachment of the anterior layers of the iris (iridoschisis) is reported. The previously reported cases are listed. No specific cause can be assigned to this unusual degenerative condition.

7075 Jenkins Arcade (22).

We wish to express our appreciation to Mr. James N. Baker who prepared the excellent illustration of this case.

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CORRELATION OF MICROSCOPIC AND SLITLAMP EXAMINATIONS OF DEVELOPING HEREDITARY CATARACTS IN MICE*

GEORGE K. SMELSER, PH.D., AND LUDWIG VON SALLMANN, M.D.
New York

A strain of Swiss albino mice which invariably develops hereditary cataract at an early age was placed at our disposal by Professor Landauer of the University of Connecticut. This stock appeared to be of normal, vigorous animals with the exception of the lens pathology to be discussed, and a deformity of all four feet which is inherited as a recessive character, called brachypody by Landauer. There is no reason to believe that this latter condition has any relation to the cataract formation.

It was planned to follow the progress of developing cataracts in these mice both by clinical study with the slitlamp and histologic examination, and to attempt correlation of the data obtained by the two methods. In addition, some preliminary studies were made which might suggest other approaches to the problem of the mechanism of the cataractous process. For these purposes a colony of animals was established, maintained on our stock diet supplemented with one based on growing chick mash with added vegetable and cod-liver oil and brewers' yeast. A control group of mice, also of the Swiss albino strain, but which is regularly free of the lenticular abnormalities, was maintained under the same conditions to provide normal material for comparison.

One hundred and five mice were examined, 70 of them on several occasions with the slitlamp and corneal microscope by one of us (L. v S.). Twenty-five of these were killed at various stages for microscopic study. The lenses of eight normal mice of various ages were also studied microscopically. Most of the sections were prepared by the celloidin method, 8 and 10 microns in thickness, and stained by standard procedures. Frozen preparations were made of 14 eyes and the sections examined for fat, cholesterol (Schultz reaction), and birefringent material.

OBSERVATIONS

The lenses appeared to be normal during the first 35 to 40 days of life. Occasionally fine remnants of the hyaloid vascular system were seen at the posterior surface of the lens but not in greater frequency or size than in normal mice of the same age. In two mice, both 39 days old, an irregularity of the specular reflex and a fine stippling were noted at the posterior pole with slitlamp examination. This appearance may be normal.

One of these lenses appeared to be quite normal when studied histologically, but the other three showed some deviation from the appearance of normal control lenses. This was evidenced by (1) the presence of small basophilic patches in the cortex near the posterior pole, (2) slight disorganization of the lens fibers at the posterior pole of the lens nucleus, (3) lack of preciseness in the posterior boundary of the nucleus (fig. 2).

It will be noted (fig. 2) that the lens abnormality involves the posterior border of the lens nucleus, very deeply stained, and all of the posterior cortex at this point. The posterior cortex (neutrophilic in staining reaction) appears to be slightly narrower than normal so that the nucleus lies nearer to the posterior pole than normally.

By 55 days of age cataracts were generally quite definite. The typical appearance seen clinically in this age group began with a circle of tiny gray dots around the posterior pole in the cortex of the lens, which was the earliest stage indentifiable as abnormal. A section of this lens is shown in Figure 3. The

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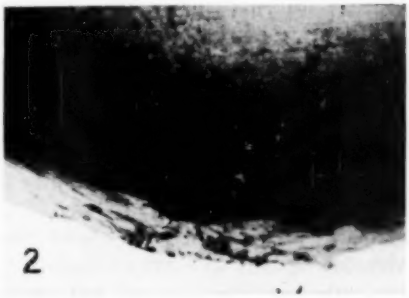


Figs. 1 to 5 (Smelser and von Sallmann). 1. Section of normal mouse lens.

2. Section of lens showing definite deformation at the posterior pole. Slight stippling, regarded as probably normal, was seen in this region with the slitlamp. Note the presence of some remnants of the hyaloid vascular pattern. Age of mouse 39 days.

3. Section through posterior pole of a lens which showed the earliest stage identifiable as abnormal by slitlamp examination. Note the very narrow cortical zone and the disruption of the more central fibers. Age of mouse 55 days.

4. Clinical appearance of an early stage in the cataract development. The opacity lies at the posterior pole of the lens. Age of mouse 66 days.

5. A slightly more advanced stage in the cataract formation. Age of mouse 66 days.

fibers of the posterior portion of the nucleus appear to be swollen and separated.

In addition, marked, though small, opacities were found clinically in the posterior polar region of other animals of this age group. They ranged from triradiate localized opaque masses to irregularly shaped opacities sometimes containing minute vacuoles. The clinical appearances of two such types are shown in Figures 4 and 5.

The histologic appearance of such an opacity, although represented by an older case, is shown in Figure 6. These opacities increase in size and density and often extend into the adjoining layers as a gray veil with fine striations. This veil could not be identified in histologic preparations.

In the further development of the cataract, irregular opacities appeared in the perinuclear area, as seen with the slitlamp, and, in some cases, minute vacuoles which seemed to lie in the subcapsular zone. Microscopic study of these lenses revealed a pyramidal homogeneous mass at the posterior pole very like that seen in earlier stages (fig. 6). The basophilic lens nucleus appeared to be displaced posteriorly and surrounded by cortex with a neutrophilic staining reaction. Around this zone was a markedly crescentic basophilic area, wide anteriorly and tapering rapidly toward the posterior pole.

On the anterior surface of this crescent were a row of small vacuoles (fig. 7). The lens cortex appeared to be normal. When the opacity involved the perinuclear zone it often formed a rather homogeneous layer around the nucleus which appeared clear. In other instances, a second more peripheral opaque zone became visible, separated by a clear interval from the more central layer. The histologic appearance of the anterior portion of such a lens is shown in Figure 7.

Finally, in a third group of animals the nucleus became cataractous before the layers of peripheral opacity developed. Sometimes a thin, dense sheath surrounded the nuclear opacity as shown in Figure 9. The further progress of the cataract was apparently not influenced by the character of the intermediate state.

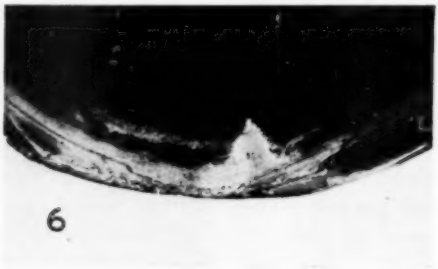
Vacuoles occurred frequently, but only in animals three months of age or older. In most cases these vacuoles appeared to be empty, but in a few they contained a stainable coagulum. Such a vacuole is shown in Figure 8. This vacuole was not noted in the slitlamp examination, but small subcapsular vacuoles were. These, on the other hand, were not found microscopically.

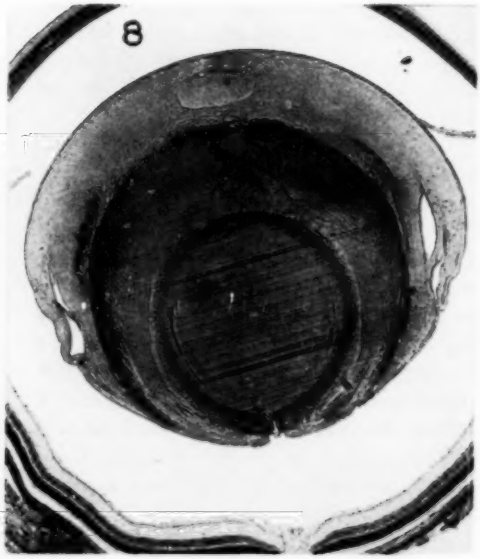
A water cleft was also noted in this eye in the slitlamp examination, and a cleft occurred at the anterior pole of the basophilic perinuclear zone. This cleft contained a homogenous material which stains very like the perinuclear material, although no structure is apparent. Many of the larger vacuoles, seen with the slitlamp, were arranged equatorially, as shown in Figure 9, although in some they appeared to fill the entire anterior part of the lens (fig. 10).

In practically all cases the lens was found to have ruptured at the posterior pole and the nucleus extruded into the vitreous. This occurred first at 70 to 80 days of age, although all animals were not so affected at this time. In older mice this phenomenon was almost invariable.

The extrusion of the lens nucleus was not obvious in the slitlamp examination, possibly because more anteriorly placed opacities obscured the view. The extrusion of the lens is not a technical artefact occurring during the histologic procedures, for it could be demonstrated by dissection of the globe prior to fixation. Such a lens is shown in Figure 11. Cataractous but intact lenses dissected out of the eye and placed in fixatives did not rupture.

Figure 8 shows what may be a very early stage in lens extrusion. The capsule is broken at the posterior pole and the lens nucleus appears to be slightly protruding. The typical appearance of these later stages is shown in Figure 12. The capsule has ruptured, and its





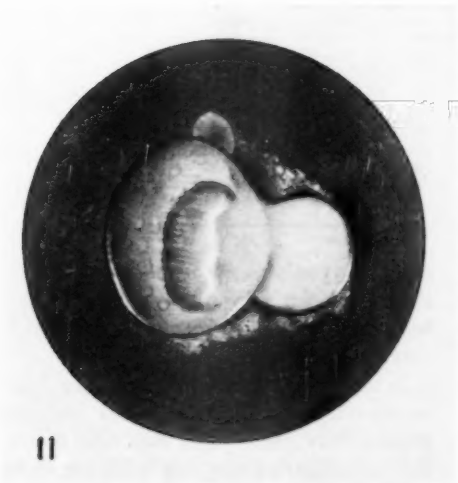
Figs. 6 to 8 (Smelser and von Sallmann). 6. Section through the posterior part of a cataractous lens showing the histologic appearance of an opacity similar to those shown in Figures 4 and 5, although it is from an older mouse, aged 125 days.

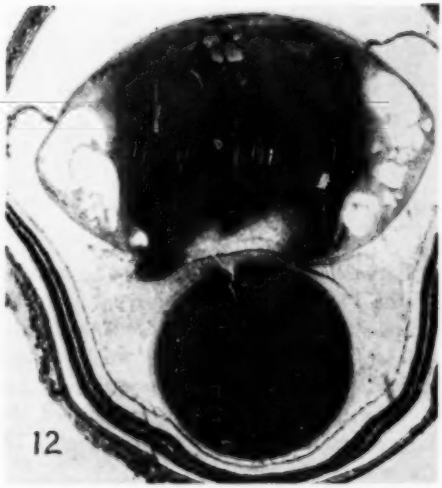
7. Anterior portion of a cataractous lens showing a row of small vacuoles lying deep in the cortex on the surface of a basophilic crescent-shaped band of material anterior to, and separated from, the lens nucleus. Age of mouse 125 days.

8. Section of a cataractous mouse lens, age of mouse 146 days, showing a coagulum filled vacuole in the anterior cortex, not noted in slitlamp examination. The nucleus appears to have been displaced posteriorly. The posterior lens capsule may have ruptured. This appears to be a very early stage of nuclear extrusion.

broken ends coil like a watch spring on either side of the opening. A dense basophilic mass, the remnant of the crescent of perinuclear material shown in Figure 7 was retained within the capsule and probably interpreted clinically as opaque nucleus.

After it was known that the lens frequently ruptured, evidence of that fact could be obtained on slitlamp examination by noting a flattening in the anterior surface of the lens and an increase in the depth of the anterior chamber.





Figs. 9 to 12 (Smelser and von Sallmann). 9. Clinical appearance of a more advanced cataract showing many equatorial vacuoles. Age of mouse 95 days.

10. An extreme case of vacuolation of the cataract. Age of mouse 219 days.

11. Drawing of a ruptured lens dissected from the eye showing the extruded nucleus. Vacuoles can be seen in the equatorial region. Age of mouse 146 days.

12. Section of a lens after rupture of the capsule and extrusion of the lens. The retained deeply staining material was opaque and obscured the extruded nucleus in the slitlamp examination. The vacuoles are similar to those shown in Figures 9 and 11. Age of mouse 125 days.

Due to the relatively small volume of vitreous and large lens in mice eyes, the extruded lens nucleus and lenticular material often came into contact with the retina. Various degrees of retinal reactions were observed. Aggregations of small cells with deeply staining nuclei, possibly lymphocytes, were frequently found. The ganglion cells were sometimes misshapen or unrecognizable. In one case, elongated spindle-shaped cells,

similar to fibroblasts were found. Of the 12 eyes examined all but three showed some retinal abnormalities. In the three which did not, the lens material was not in direct contact with the retina. These may have been cases in which the lens was very recently ruptured.

lenses in which no crystals had been noted. In one case there was an agreement, in that neither cholesterol nor crystals were found.

The histochemical test for cholesterol and the slitlamp examination report on the crystals were in agreement in 50 percent of the cases. It should not be concluded from this

TABLE 1

CORRELATION OF IRIDESCENT CRYSTALS WITH THE HISTOLOGIC DEMONSTRATION OF FAT AND CHOLESTEROL IN THE LENS

Animal and Eye	Age (months)	Slitlamp	Microscopic Section	
		Iridescent Crystals	Cholesterol (Schultz Reaction)	Fat (Sudan Positive)
122 O.S.	4½	−	+	+
20 O.S.	6	−	+?	+
21 O.D.	6	−	+	+
82 O.S.	8½	++	++	+
82 O.D.	8½	+	+?	+
113 O.D.	9	−	+	++
83 O.S.	9	−	−	−
83 O.D.	9	+	+	+
1 O.S.	11	−	+?	+
3 O.S.	11	+	++	++
62 O.S.	12	++	+	+
62 O.D.	12	++	+	++
4 O.S.	old	++	−	−
4 O.D.	old	+	−	−

Fat stains (Oil red O) applied to sections of the 14 eyes fixed in 3-percent formalin revealed considerable fat in droplets of variable size. These fat droplets would appear as vacuoles in the celloidin preparation, but it is certain that most, if not all, of the larger vacuoles, such as shown in Figure 12, did not contain fat.

In many instances cataracts of mice eight months or older were seen with the slitlamp to contain iridescent crystals which are usually considered to be cholesterol. These crystals had been noted in eight of the 14 eyes at the time of autopsy. No crystals were noted in the other six eyes. A histochemical test (Schultz reaction) for cholesterol was carried out on all sections and the results are given in Table 1.

Cholesterol was identified in six of the eight lenses in which the crystals were seen, however, cholesterol was also found in five

that the crystals do not necessarily represent cholesterol, for they may occasionally have been obscured in the slitlamp examination by overlying opaque masses.

In those cases where they have been found in vivo and no cholesterol was identified histologically, the crystals may have been so fine and dispersed that they were not visible in the sections. However, in these cases all of the sections cut from the eye were subjected to the Schultz reaction in order to discover isolated minute deposits of cholesterol, which was usually associated with fat and located in microscopically visible droplets.

It may be noted that cholesterol and fat were always found in the same lenses and as early as four and one-half months, whereas the iridescent crystals were not observed in animals younger than 8½ to 9 months of age.

The rupture of the lens capsule in this

type of cataract suggested that the thickness of the capsule should be investigated in lenses prior to its break at the posterior pole. Accordingly anterior and posterior capsule thicknesses were determined in a series of lenses of normal and cataractous mice. The measurements, made with an ocular micrometer, of the anterior capsule are much more precise than those of the posterior capsule. Each value given in Table 2 is the average of measurements of several sections and shows

gested to us that the lens epithelium might also show abnormalities. Qualitative examination of the epithelium of early cataractous, unruptured lenses revealed no obvious peculiarities. The central portion of the lens epithelium occasionally stained poorly and the nuclei seemed to be rather far apart. Accordingly nuclear counts were made in representative sections of a number of lenses from normal and cataractous mice. These sections were then projected at ×100 magni-

TABLE 2

THICKNESS OF THE LENS CAPSULE OF NORMAL AND CATARACTOUS LENSES

Normal				Cataractous			
Mouse and Eye	Age (days)	Thickness of Capsule		Mouse and Eye	Age (days)	Thickness of Capsule	
		Anterior (microns)	Posterior (microns)			Anterior (microns)	Posterior (microns)
106 O.D.	39	5.0	1.82	101 O.D.	39	4.2	1.8
106 O.S.		5.0	1.6	101 O.S.		4.6	1.8
107 O.D.	39	5.0	2.16	103 O.D.	39	4.2	1.6
107 O.S.		4.5	2.5	103 O.S.		4.0	1.4
				97 O.D.	55	5.16	1.72
				97 O.S.		6.0	1.6
				98 O.D.	55	5.6	1.0
108 O.D.	71	5.6	2.0	98 O.S.		6.0	1.0
108 O.S.		6.0	2.16	18 O.S.	70	8.0	1.0
109 O.D.	71	8.0	1.8	172 O.D.	86	6.12	0.92
109 O.S.		7.0	2.0	172 O.S.		5.6	—
313 O.D.	125	8.2	2.0	150 O.S.	113	6.9	3.2
313 O.S.		7.8	2.2	44 O.D.	125	6.2	1.8
314 O.D.	125	8.7	2.2	44 O.S.		9.0	1.7
314 O.S.		8.0	2.04				
316 O.D.	145	9.2	2.6	45 O.S.	146	7.4	1.1
316 O.S.		8.9	2.74				

Mice No. 101 and No. 103 appear clinically normal or very nearly normal.

that the lens capsules of mice of the cataractous strain are thinner than normal before a change in the lens can be seen with the slit-lamp.

This difference in the anterior capsules continues when the opacity of the lens becomes marked, but the posterior capsule becomes even thinner, in most cases, until it breaks. Of course, if the lens is swelling prior to its rupture, the capsule may be passively thinned by stretching. However, this process presumably is not very far advanced in mice whose lenses are still clinically normal at 39 days of age.

The thinning of the lens capsules sug-

fication and the length of the epithelium measured in millimeters.

All of these sections were 10 microns in thickness. The number of nuclei counted was divided by the length of the section of epithelium in which they were located to give the relative density of the cellular population in a known area of lens epithelium. These data, (table 3), although somewhat variable, show that there were about 25 percent fewer cells in a unit area of the lens epithelium in the cataractous mice. The data are not sufficient to determine whether a deficiency in epithelial cells existed in the very earliest stages and, therefore, it cannot

be concluded that the sparseness of the epithelial population is a primary or a secondary phenomenon resulting from stretching of the epithelium, if indeed this does occur.

Whatever the nature of the earliest changes in this or other cataract development may be, there is general agreement that the proportion of soluble proteins in the lens decreases. It was thought that, by electrophoretic analysis of the soluble lens proteins of early and late cataracts, a suggestion could be had indicating which of the lens proteins are reduced. Accordingly pooled lots of (A) normal mouse lenses, (B) lenses from the cataractous strain showing incipient lens changes, and (C) advanced cataracts were used. Since the amount of soluble lens protein in these three groups was both small and unknown, a large number of mice were used, particularly of Group C.

The lenses were thoroughly ground in phosphate buffer pH 7.4 and the insoluble protein removed by centrifugation. The clear supernatant was used for analysis without dialysis or other treatment.* Nitrogen determinations† were made on aliquots of the solutions submitted for electrophoretic analysis. These experiments were carried out twice—a total of six analyses of pooled groups of lenses. The mice in Groups A and B were of the same age.

Three electrophoretic patterns are shown in Figure 13. The size of the pattern is proportional to the concentration of the protein solution submitted and is, therefore, of no significance here. The area occupied by each of the several components is also proportional to the concentration of the protein, and the proportion each makes up of the whole is of importance.

Three major protein fractions were found in each sample of lens protein. The ratio of the quantity of these three in the normal, from the slowest to the fastest, is 2.6 : 1.0 : 1.3. When similar ratios were constructed for the early cartaracts a marked decrease in the amount of the slow component was immediately seen, 1.27 : 1.0 : 1.2. The pattern given by the proteins of the advanced cataracts also showed a marked reduction in the slow component, with no change in the other two, relative to each other.

TABLE 3

NUMBER OF NUCLEI IN THE LENS EPITHELIUM OF NORMAL AND CATARACTOUS MICE

Normal				Cataractous			
Mouse No.	Age (days)	*Number of Nuclei / Length of Epith. ×100		Number of Nuclei / Length of Epith. ×100	Age (days)	Mouse No.	
106	O.U.	39	86	72	39	101	O.D.
107	O.U.	39	78 (peripheral sections)	77	39	103	O.S.
				46	55	97	O.S.
108	O.U.	71	89	58	71	18	O.S.
109	O.U.	71	73	66	71	18	O.D.
				75	86	172	O.S.
				68	86	172	O.D.
313	O.U.	125	70	37	113	150	O.S.
314	O.U.	125	71	52	125	44	O.D.

* Number of nuclei = the number counted in 3 to 4 sections. Length of epithelium = the length of the epithelium measured in a drawing made at ×100 magnification by projection. This figure was multiplied by 100 to delete the decimal fraction. All counts were made on 10 μ sections.

* We wish to express our thanks to Dr. Dan H. Moore of the Electrophoresis Laboratory, College of Physicians and Surgeons, Columbia University, for the electrophoretic analyses.

† We are indebted to Dr. Zachary Dische and his staff of the Biochemistry Department of Ophthalmology for the nitrogen determinations.

Nitrogen determinations showed that there was 62.9 percent less soluble protein in the advanced cataracts than in the normal. The slow component forms 52.9 percent of the soluble lens proteins in the normal lens and is reduced to 34.7 percent in the advanced cataracts. It is evident, therefore, that, although this reduction accounts for a large measure of the protein loss, it cannot account for all of it. The middle and fast components are therefore affected about equally by some proteolytic process, but at a rate much slower than that attacking the slow component.

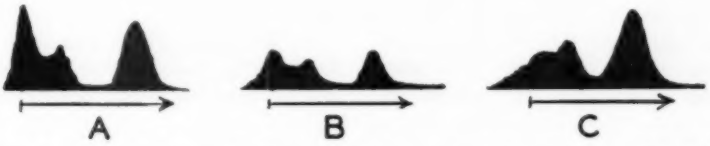


Fig. 13 (Smelser and von Sallmann). Electrophoretic patterns of the soluble proteins of (A) normal mouse lens, (B) early cataract, and (C) late cataract. The reduced size of the pattern in (B) is due to the amount of protein in the sample which was analyzed. The slow component is on the left.

The reduction in quantity of the slow component in the advanced cataracts was 76 percent, of the middle 47 percent, and of the fast 48 percent. This effect on the proteins was marked even in the early stage investigated. The rates at which these three components moved in the electrophoretic field was not different in the several samples tested, indicating that the proteins present in the cataracts were the same as those found in normal lenses, although their proportion to each other and their quantity had been altered.

Discussion

The cataract discussed here does not apparently have a counterpart which is common in man. E. Treacher Collins[1] described a few cases of posterior cortical cataract with rupture of the capsule at the posterior pole. Ziegler[2] described an hereditary posterior polar cataract which in the earliest stages seems somewhat similar to that studied here. Some features of the cataract under discussion are reminiscent of posterior lenticonus.

Patry, quoted in Collin's article, commented on the apparent displacement of the lens nucleus to the posterior pole of the lens. A similar condition was noted in this strain of mice. However, the hyaloid vessels appear to play no rôle in the weakening and distortion of the posterior part of the lens as has been suggested that they may in man. The hyaloid system did not seem unusually persistent in these mice and had disappeared entirely in all cases in which a rupture of the capsule had occurred.

The sequence of changes in these lenses was somewhat variable and marked differences sometimes occurred between the eyes of an individual. Completely normal lenses were found up to two months of age. Faint opacities were, however, detected as early as the 17th day of age and, in one case, as late as nine months. Dense opacities were usually present by 70 days of age. Vacuoles were not common until after the third month, by which time most of the lenses had ruptured and the nucleus had been extruded.

The occurrence of cholesterol in these cataracts is not surprising and has been reported in cases of hereditary cataract[3] The cholesterol appears late in the process and probably represents the end of a degenerative change rather than an early or an active phase.

The cause of swelling or even its occurrence has not been demonstrated in these studies, but the thinning of the capsule ap-

pears to be an early, definite morphologic change.

Electrophoretic analysis of normal beef, horse, and pig-lens proteins have been made by Viollier, Labhart, and Süllmann.[4] These analyses, carried out in veronal-acetate buffer, pH 7.9 with an ionic strength of 0.1 showed only two major components. Our analyses of normal mouse lenses clearly showing three major components of the soluble lens proteins were made in phosphate buffer at pH 7.4 with an ionic strength of 0.2. One additional analysis, however, was made with barbiturate buffer at pH 8.6 with an ionic strength of 0.1, which also revealed three components. The differences between the observation of Viollier and others and the present ones may be due to variation between the species or to the greater solubility of some proteins in salt solutions, since they used water in making the lens extract instead of buffer, as in our case.

It is impossible at the present time to identify the three components shown in the electrophoretic analysis of the mouse lens with the α and β crystalline or albumen found in other lenses by chemical methods. The relative vulnerability of one of the components (slowest) to the cataractous process recalls immediately, however, the studies of Krause,[5] who showed that β crystalline was rapidly attacked by proteolytic enzymes, in a slightly acid medium, whereas α crystalline was relatively stable.

Summary

1. Morphologic changes, observed clinically and histologically, in a developing hereditary cataract have been described and compared.

2. The earliest observed changes involve slight disorganization in the posterior cortex and thinning of the lens capsule.

3. Decrease in the number of lens epithelial cells per unit area was noted in early cataracts.

4. Vacuolation of the lens and rupture of the capsule, thus discharging lens material into the vitreous cavity, were regularly observed.

5. The observation of iridescent crystals in the lens could not be well correlated with the demonstration of cholesterol histochemically.

6. Electrophoretic analysis of normal mouse-lens protein revealed three major components.

7. One lenticular component is reduced, in the formation of this cataract, at a rate nearly twice as great as that affecting the other components.

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Discussion

Dr. Wilhelm Buschke (New York): I should like to ask two questions in relation to this very interesting presentation.

The first question has to do with the problem of reduction of cell divisions in the epithelium. Was there any reduction in the thickness of the lens at any stages preceding the actual cataract, as compared with control animals at a comparable age?

The second question is in relation to your

finding that the lens capsule was thin. Were there any histochemical changes in the lens capsule, particularly in relation to the sulfate polysaccharide, for example, with metachromatic staining? If so, it would be interesting to speculate about the possible connection of these changes with the skeletal changes, on the basis of a common biochemical factor.

DR. GEORGE K. SMELSER (New York): If I understood Dr. Buschke correctly, his question was on mitotic activity. There were some mitoses found, but we made no count of mitotic figures in the lens capsules of either the normal or the cataractous.

The number of cells present in the very early stages was reduced in the cataractous strain, but not by 25 percent; it was reduced on the order of 10 or 12 percent in numbers. I did not give the figures because I don't think one should give them undue emphasis, because they were based on rather few cases. These observations were made in animals prior to the development of a clinically observable cataract or a clinically observable abnormality. The thickness of the capsule was definitely less before there was any clinically observable abnormality.

DR. BUSCHKE: I meant the thickness of the lens.

DR. SMELSER: The whole lens? I cannot answer that, except in this sense: In histologic sections there was no change. I would not have too much confidence in measurements made on them. I would prefer to have the volume differences here. There was no obvious change in the sections. We made no histochemical studies on lens capsule. We hope to get some stimulation and ideas on that later today.

CYCLODIALYSIS*

I. A DISCUSSION OF TECHNIQUES

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The modus operandi of the cyclodialysis operation for glaucoma, according to Heine's original concept,[1] was the establishment and maintenance of a communication between the anterior chamber and the suprachoroidal space. Proof that this communication persisted was furnished by Elschnig[2] in 1932 and Barkan[3] in 1947 from microscopic examination of sections of eyes in which successful cyclodialysis operations had been made but were removed post mortem. Further evidence in favor of this idea was found clinically upon gonioscopic examination by Barkan, Boyle, and Maisler[4] in 1936 and Burr[5] in 1947. The latter observer found that a cleft, indicating a separation of the ciliary body from its scleral attachment, could be demonstrated† in the chamber angle in all successful cases of cyclodialysis. The size of the cleft apparently had little to do with the degree of reduction of the intraocular pressure. As long as one was visible, the intraocular pressure was within normal limits.

According to Heine's description of his operation, an incision 3-mm. long was made through the sclera approximately 6-mm. posterior to, and parallel with the limbus. A spatula was inserted between sclera and ciliary body through the incision and passed into the anterior chamber to a depth of approximately 3 mm. The spatula then was

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† Burr found that in some cases it was necessary to constrict the pupil with a strong miotic in order to view the cleft in the angle over the iris hump.

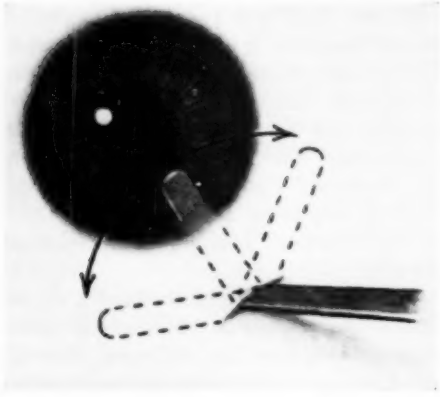

Fig. 1 (Lee and Allen). Heine's technique of cyclodialysis (after Blaskovics and Kreiker).

swept backward into the chamber angle (fig. 1). After breaking the attachment of the ciliary body to the scleral spur, it was then passed into the suprachoroidal space, first on one side and then on the other.

Blaskovics[6] pointed out that this method unduly traumatized the iris and ciliary body. It was possible for the spatula to tear through the base of the iris especially in cases with peripheral anterior synechias, or through the anterior portion of the ciliary body before breaking into the suprachoroidal space. This favored hemorrhage and postoperative iritis with stimulation of scar-tissue formation and subsequent obliteration of the newly created cleft thus sealing off the outlet for the aqueous humor from the anterior chamber into the suprachoroidal space. In order to minimize this, Blaskovics in 1935[6] introduced his modification which has become known as the inverse method of cyclodialysis (fig. 2). He reversed the Heine technique, separating the ciliary body from its attachment by sweeping the spatula from the suprachoroidal space into the anterior chamber. Thus, according to Shaffer,[7] the spatula followed a natural line of cleavage.

Since 1931, O'Brien[8] has been using and teaching a multiple thrust method of performing an inverse cyclodialysis. He made the scleral incision 5 mm. posterior to and parallel with the limbus. From this point he passed a spatula between sclera and ciliary body into the anterior chamber until the tip was just visible, then withdrew and reinserted the tip into the chamber at progressively adjacent points, first to one side of the incision then to the other, until approximately half of the circumference of the ciliary body was detached from the scleral spur.

Although excellent results have been obtained by these last two techniques, annoying hemorrhages have still occurred occasionally and, when extensive, they have jeopardized the success of the operation. Therefore a slight modification of the O'Brien technique was made in an effort to reduce the incidence of hemorrhage even further (figs. 3a to 3e and 4).

Anatomic considerations

The choroid and ciliary body are in loose apposition with the sclera except at three main points. The choroid is firmly attached to the sclera in the vicinity of the optic nerve

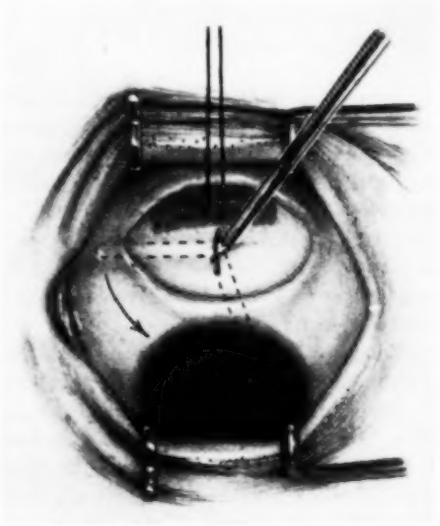

Fig. 2 (Lee and Allen). Blaskovics's technique of inverse cyclodialysis (after Blaskovics and Kreiker).

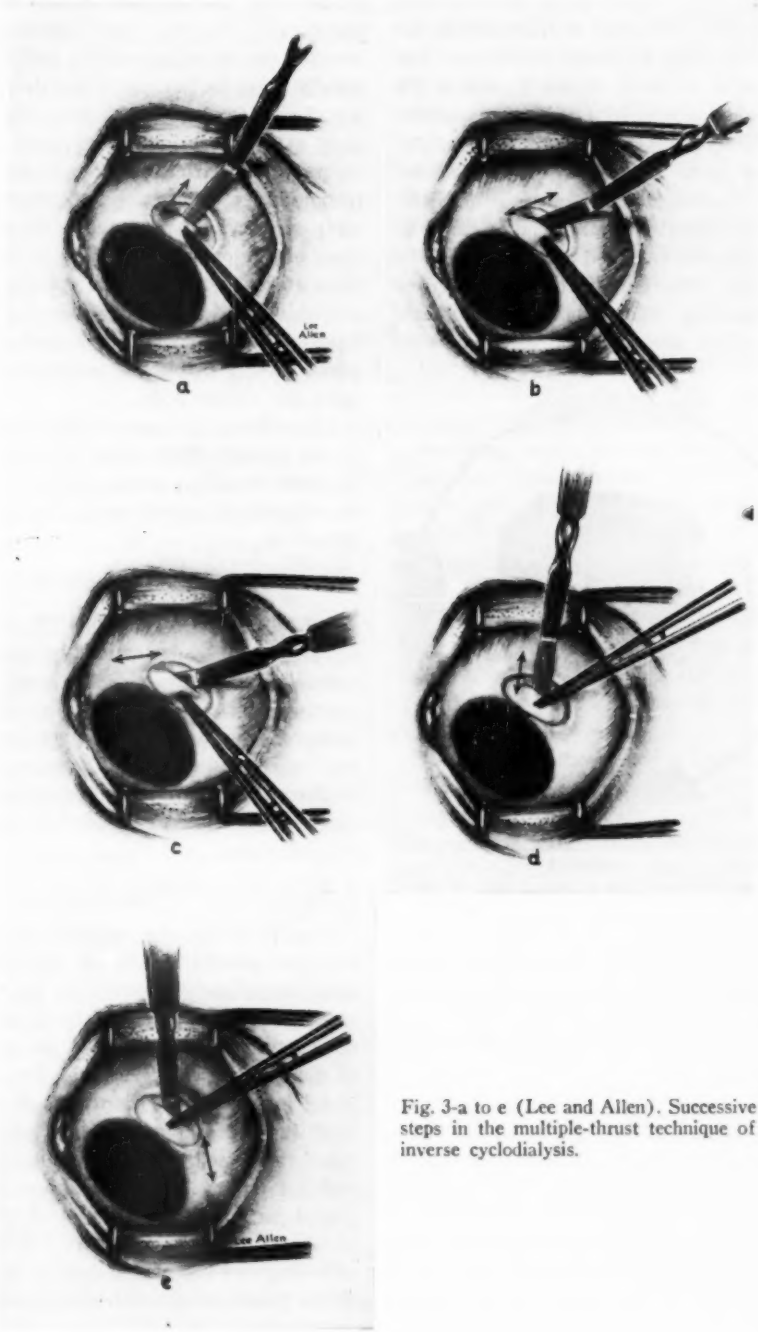

Fig. 3-a to e (Lee and Allen). Successive steps in the multiple-thrust technique of inverse cyclodialysis.

where the ciliary vessels pierce the sclera and also it is firmly attached to the sclera at the exits of the venæ vorticosæ posteriorly. The ciliary body is firmly attached only at the scleral spur anteriorly. Over the remainder of the choroid and ciliary body is the suprachoroidal space through which nonvascular lamellae of connective tissue run in all directions. The lamellae contain elastic fibers as well as pigment cells and are surrounded by endothelial cells, thus forming a maze of interconnecting endothelial-lined potential spaces called the suprachoridal lymphatic

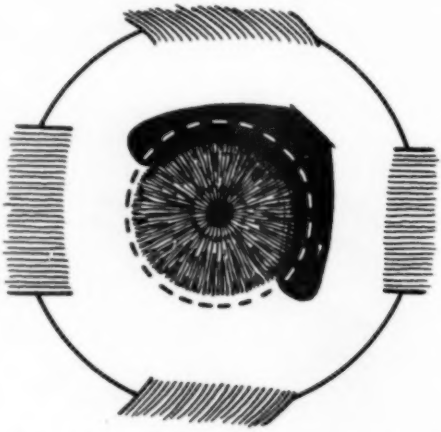

Fig. 4 (Lee and Allen). Extent of excursion of cyclodialysis spatula indicated in solid black. Dotted line indicates line of attachment of ciliary body to scleral spur.

space of Schwalbe. The lamellae are fewer in the region of the ciliary body and steadily decrease from behind forward. The most anterior reaches of the suprachoroidal space immediately behind the scleral spur seem entirely empty.[9] The ease with which the choroid becomes separated from the sclera is illustrated by the large number of cases of choroidal detachment seen after cataract extraction.[10]

The blood supply of the uveal tract is derived from three sources: (1) The 10 to 20 branches of the short ciliary arteries which enter the choroid around the optic nerve; (2) the two long posterior ciliary arteries, one traveling nasally and one temporally along the horizontal meridan between the choroid and retina to enter the ciliary body at its posterior border; and (3) the anterior ciliary arteries coming from the four recti muscles. There are two arteries from each except the lateral rectus from which there is only one. These vessels travel across the tendon insertions in the episcleral tissue to within 2 to 4 mm. of the cornea, then each sends a large perforating branch into the sclera passing through it perpendicularly to enter the ciliary body.

The venous drainage of the unveal tract occurs through the four venæ vorticosæ and the anterior ciliary veins which accompany the anterior ciliary arteries as they perforate the sclera.

Technique of cyclodialysis

1. Choice of site of operation

This should be determined by gonioscopic examination of the chamber angle before operation, whenever possible. It is desirable to avoid dense anterior peripheral synechias and large blood vessels in the angle. In cases of glaucoma following cataract extraction the cyclodialysis should be made below to avoid the scar tissue.

2. Preparation of operative site

Usually either the superior or inferior temporal quadrant is chosen. Incision in the area immediately anterior to the superior rectus muscle as described by Blaskovics is not recommended because of the proximity of the anterior ciliary vessels. The sclera is bared by a short incision through the conjunctiva and Tenon's capsule. All visible episcleral vessels are cauterized with a thermal hot point. A scleral fixation suture is placed just anterior to the site of the scleral incision. It may be held either with a pair of forceps or a hemostat and the movement of the globe is thus controlled easily.

3. The scleral incision

In the Heine, Blaskovics, and O'Brien techniques the scleral incision is placed 5 to 6 mm. back of the limbus. Barkan and others[4] suggest that it be placed even further back in order to obtain a more extensive dialysis of the ciliary body. By placing the scleral incision 6 mm. or more back from the limbus, not only will it permit a sufficient length of spatula to be introduced into the suprachoroidal space to dialyze the ciliary body, but according to Salus[11] and Meller[12] it will also permit the spatula to section the nerves and vessels supplying the ciliary body as it sweeps through the suprachoroidal space, thus reducing formation of aqueous humor through atrophy of the ciliary body. Furthermore, should the ciliary body be injured while making the scleral section in this region, the less important nonvascular pars planum will be involved and not the more important pars ciliaris.

More recent studies, however, indicate that the disruption of nerve and blood supply to the ciliary body in the cyclodialysis operation contributes little if anything toward its success. In fact, rupturing the blood vessels should be avoided. Furthermore, one can dialyze half the circumference of the ciliary body without having to place the scleral incision farther back as recommended by Barkan and others, if one uses the multiple thrust technique of O'Brien instead of the sweeping techniques of Heine and Blaskovics.

Therefore, we prefer to place the incision approximately 3 mm. back from the limbus. By traction on the fixation suture, the scleral incision can be made safely, with danger of injury to the ciliary body reduced to a minimum. Traction on the suture actually lifts the sclera away from the ciliary body as the incision is being made.

4. The cyclodialysis

By traction on the scleral fixation suture, the spatula can be introduced through the scleral incision into the suprachoroidal space with ease. After a very short distance, the spatula reaches the scleral spur. With firm but gentle pressure, keeping the spatula against the sclera, the dialysis is made and the tip of the spatula may be seen just within the inner margin of the limbus. It is slightly withdrawn and a series of short thrusts are made with the spatula always confined to the immediate region of the limbus and scleral spur. Approximately half the circumference of the ciliary body is separated from the scleral spur.

The cyclodialysis may involve the upper half, the lower half, or the temporal half of the ciliary body or, if the occasion demands it, the nasal half. The spatula is not permitted to enter the anterior chamber for more than 0.5 to 1 mm., nor is it swept backward into the suprachoroidal space. Its movements are limited to the immediate vicinity of the scleral spur. One need not fear performing a cyclodialysis past the horizontal meridan in order to avoid rupturing the long posterior ciliary arteries if one uses this technique. With the Heine or Blaskovics technique, one should avoid this region.

Even with the utmost care in technique and freedom from complications, there is a strong tendency for a narrow cyclodialysis to become reattached. The reason for performing a wide cyclodialysis is, then, not to obtain a large, filtering cleft but, by obtaining an extensive dialysis of the ciliary body, to reduce greatly the tendency for a complete reattachment, and to leave in a large percentage of cases, a small but adequate functional cleft in the chamber angle.

Comment

The purpose of the cyclodialysis operation is to permit internal drainage of the aqueous humor into the suprachoroidal space. This is accomplished when the attachment of the ciliary body to the scleral spur is severed. Further excursion of the spatula through the suprachoroidal space over the ciliary body

region is unnecessary since the ciliary body posterior to the scleral spur is in loose apposition with the sclera, and fluid can flow through this area without the help of instrumentation. This maneuver increases the amount of trauma to the ocular tissue.

Breaking of the perichoroidal lamellæ together with irritation of the ciliary body as the spatula sweeps over it might account for the severe iridocyclitis that sometimes follows a cyclodialysis operation. It certainly does result in a higher percentage of hemorrhages and more severe ones. Either of these conditions may be reasons for failure of the operation. Furthermore, in both the Heine technique and Blaskovics's modification, the spatula is carried into the anterior chamber for a considerable distance. This requires a skillful operator to avoid trauma to the iris and damage to the posterior surface of the cornea, especially when the chamber is shallow.

We are in full agreement with Barkan, Boyle, and Maisler that at least two fifths of the circumference of the ciliary body should be dialyzed to get the best results. O'Brien[13] recently has reëmphasized this and advocated approximately one half the circumference. However, one need not make the incision more than 3 mm. back from the limbus to accomplish this.

In cases with very shallow anterior chambers, we have performed a peripheral basal iridectomy together with the cyclodialysis. This additional procedure not only decreases the opportunity for formation of anterior peripheral synechias with resultant closure of the cyclodialysis cleft, but also frequently deepens the anterior chamber all around with its attendant advantages. Unlike the Wheeler[14] technique, a second incision is not necessary to perform the basal iridectomy. It can be made easily through the cyclodialysis incision since that is so near the limbus. In fact, to facilitate further the performance of the iridectomy, should this additional step be contemplated, the scleral incision should be made less than the usual 3 mm. back of the limbus.

Summary

A method of inverse cyclodialysis is described in which the action of the cyclodialysis spatula is confined strictly to the region of the scleral spur. We believe this technique will reduce operative trauma with hemorrhages and postoperate irritation to a minimum and will increase the percentage of successes of the cyclodialysis operation.*

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* Case histories will be presented in later publications.

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ANISEIKONIA FOR DISTANT AND NEAR VISION

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Can the aniseikonia for near vision be essentially different from that for distant vision? Although different measurements at the two distances are often found,[1] the questions to be answered are: to what extent are those differences significant and are they due to a basic difference in the aniseikonia or are they a peculiarity of the method of measurement? The answers are important, on the one hand, to the design of the eikonometer and, on the other, to the clinician who must reduce to a minimum the time needed for the aniseikonic examination. From the physiologic point of view significant differences would be important for their possible relation to changes in astigmatism, motility, and unequal accommodation from distant to near vision. Unless unequal changes in the optical systems or in the neurologic processes of the two eyes occur, it is difficult to account for other than small differences in the aniseikonia.

The partial unreliability of the measurements for near vision on the regular (direct-comparison) eikonometer, especially in the horizontal meridian,[2] has prevented a thoroughgoing study of the problem. With the development of the space-eikonometer technique, however, a means for a cross check with the regular eikonometer is now available. A definite clarification of the problem requires the study of a large number of cases, together with a study of the reliability of the space-eikonometer. At the moment, the data available on both of these studies leave much to be desired. However, the data on 115 subjects whose aniseikonic measurements had been taken on both eikonometers for distant and near vision are to be found in the files of the more recent cases of the Dartmouth Eye Institute. Since these data constitute evidence toward the solution of the problem, they are presented in this paper.

The descriptions of both the regular (direct-comparison) eikonometer and the space-eikonometer can be found in the literature and will not be given here. It is pertinent to review only the essential differences in the two instruments.

The earlier instrument depends on the patient's making a more or less direct visual comparison of the relative dimensions of the images of a suitable target as seen by two eyes.[3-6] The target (fig. 1), which makes use of plates of polaroid for separating the images seen by each of the two eyes, consists of light details, either projected on a metallic screen or presented in a transparency.

A configuration of a vertical and a horizontal line intersecting at a central circular disc is seen binocularly (unpolarized), while two systems of opposing lines (arrows) are so polarized that one is seen by the right eye, the other by the left eye. Thus, the right eye would see the lines associated with the odd numbers only, while the left eye would see those with the even numbers only.

Each pair of opposing arrows constitutes a vernierlike device and, if there is a difference in the sizes of the images between the two eyes, any two arrows will not be aligned but rather displaced with respect to each other. By suitable optical systems the relative magnifications of the images of the two eyes can be adjusted until the patient reports that the arrows on opposite sides of the central fusion disc are aligned or are equally dis-

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placed (in case a marked fixation disparity exists).

The test constitutes, therefore, a direct comparison of the images seen by the two eyes. The sensitivity depends on the accuracy with which the fusion of the central patterns of the target is maintained, and on the visual acuity of each of the eyes. A fixation disparity, which is usually present if a phoria exists, may cause an equal displacement of the images of the arrows and may reduce somewhat the sensitivity.

The space-eikonometer[7-10] depends on binocular stereoscopic spatial localization and on the fact that an aniseikonic error changes the usual disparity relationships between the retinal images of objects in space, with the resultant incorrect spatial orientation.[11,12] As schematically shown in Figure 2, the test detail is a space configuration, consisting, first, of an oblique cross made by a pair of intersecting cords stretched at right angles to each other and mounted in the frontoparallel plane; and, second, of two pairs of smooth vertical (to the visual plane) cords supported in front of and behind the cross and parallel to it. A central cord is usually suspended through the center of the cross. The two front cords subtend a visual angle to the subject of about 12°. Carefully adjusted apertures restrict the field of binocular vision to the test elements, which are evenly illuminated and viewed against a black cloth background. All empirical clues to depth perception are thus reduced to a minimum.

For near vision (40 cm.), the cords are replaced by strands of silk thread, accurately mounted in a small box frame and attached to the eikonometer chassis. Experience has shown, however, that it is much more difficult to eliminate empirical clues to depth perception by this method at near vision, and the sensitivity of the test is found to be somewhat less than that for distant vision. However, if the test configuration is replaced by a "vectograph"[13] transparency of the same dimensions, those empirical clues are nearly eliminated and the sensitivity is only slightly less than that of

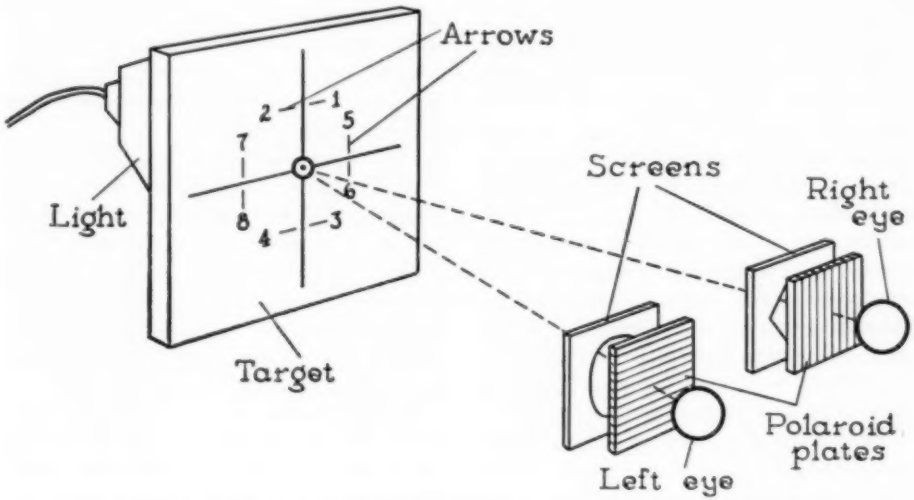

Fig. 1 (Ogle and Triller). The type of target regularly used in the direct-comparison or vernier eikonometer.

the test for distant vision. Most of the space-eikonometer data for near vision were therefore taken with the "vectograph" target.

Suitable optical systems permit the relative magnifications of the images of the two eyes to be adjusted, so that the several parts of the test configuration are perceived stereoscopically correctly oriented in space. at one visual distance have not been an influencing factor in the measurements obtained at the other visual distance.

The 115 subjects included in this report were routine patients of the Dartmouth Eye Institute who had been referred for examination of aniseikonia. In many cases an additional spherical correction was needed for the near-vision tests. These additions were

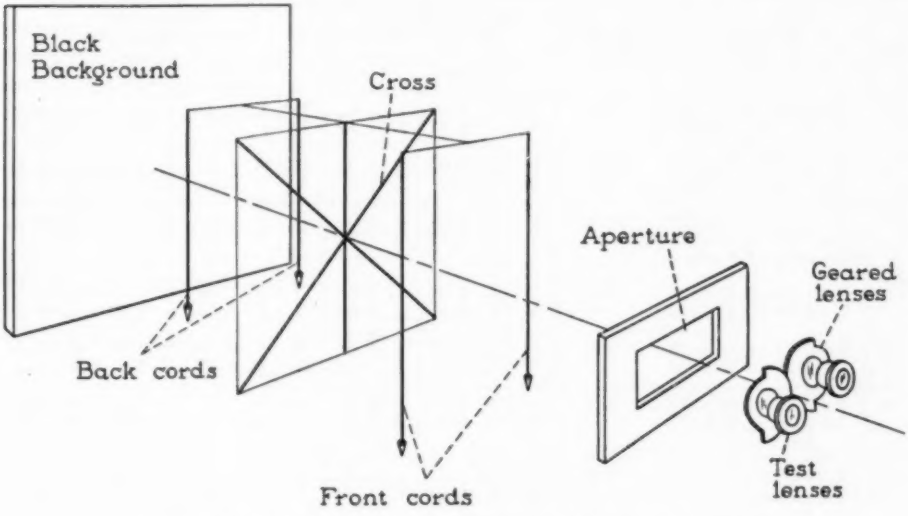

Fig. 2 (Ogle and Triller). Schematic drawing of the space-eikonometer.

The method of limits is used to determine the aniseikonic errors.

The data presented here are from the case record files for patients who have been examined on both the direct-comparison eikonometer and the space-eikonometer for both distant and near vision. Measurements to be compared are those of the aniseikonic corrections for the horizontal and vertical meridians, and the declination error.[14-16] The data were obtained by three clinicians, one of whom obtained all of the data on the space-eikonometer. Obviously, it would have been better if the measurements for near vision could have been made by a different operator. It is hoped that the data always equal spheres, carefully adjusted for equal distances from the eyes, and should not, therefore, of themselves introduce any changes in the relative magnifications of the dioptric images in the two eyes.

It is not feasible to present in this paper a table of all data obtained.* However, typical results are shown in Table 1. In this are given the refractive corrections used during the examinations, and the phoria for near vision is indicated because of its possible influence on the data of the direct-comparison eikonometer for near vision. Under the eiko-

* To those interested in studying the complete set of data, photostatic copies will be gladly sent by the authors.

nometer headings are shown the percentage magnifications that had to be introduced before the eye indicated, in order to equalize the relative magnifications of the images of the two eyes. These data are for the horizontal (H) (axis 90°) and the vertical (V) (axis 180°) meridians. For the space-

urements for distant and near vision, though less so in the horizontal meridian of the direct-comparison eikonometer, as might have been expected. For a more specific evaluation, it is necessary to study the variability between the measurements for distant and near vision of each instrument in

TABLE 1

TYPICAL COMPARATIVE EIKONOMETER MEASUREMENTS OBTAINED AT DISTANT AND NEAR VISION

No.	Refractive Correction	Phoria* Near	Direct-Comparison Eikonometer			Stereoscopic Space-Eikonometer			
				Distant	Near		Distant	Near	δ
1	R+0.62−0.62×170 L−0.25−1.12×135	5 X	H V	L 2.25 L 1.75	L 2.0 L 1.75	H V	L 2.5 L 2.0	L 2.0 L 2.0	D+0.3 N+0.8
2	R−0.25−1.50× 40 L+0.50−0.50×180	12 X	H V	R 2.0 R 1.0	R 2.0 R 2.0	H V	R 1.5 R 1.0	R 1.8 R 1.2	D+0.5 N+1.0
3	R+1.75−1.75×175 L+2.00−0.75×130 With prisms B.I. at near	18 X	H V	R 3.00 R 2.50	R 6.0 R 2.75	H V	R 3.0 R 3.0	R 2.5 R 2.4	D+0.2 N+0.7
4	R+1.00−0.25× 85 L−0.25−0.50×120	15 X	H V	L 4.0 L 2.5	L 2.0 L 2.0	H V	L 1.75 L 1.75	L 2.0 L 1.8	D+0.3 N+0.2
5	R+0.75−1.25× 10 L−0.25−0.50× 80	3 X	H V	L 1.25 R 1.0	L 1.0 R 0.75	H V	L 0.75 R 0.25	L 1.0 R 0.5	D+0.2 N+0.3
6	R+2.25−1.25×175 L+6.50−5.00× 5 Add +2.50	4 X	H V	R 6.0 R 0.5	R 10.0 R 0.5	H V	R 7.0 L 1.0	R 7.5 L 3.0	D−1.0 N−1.0
7	R+1.00 S L+1.00 S Add +1.75	2 X	H V	L 0.5 L 0.25	L 0.75 L 1.0	H V	L 1.0 L 0.5	L 0.5 L 0.5	D 0.0 N 0.0
8	R+2.00−1.25×135 L−2.00−1.50×160 Add +1.25	orth.	H V	L 3.5 L 3.25	L 2.25 L 2.5	H V	L 2.0 L 3.0	L 2.5 L 3.0	D+0.5 N+0.5
9	R−2.25−0.75×160 L Plano−1.50×180 Add +1.50	6 X	H V	R 1.25 R 1.0	R 2.0 R 0.5	H V	R 1.5 L 0.5	R 1.75 0.0	D−0.2 N 0.0

* Prism diopters.
X—exophoria.

eikonometer the correction of the declination error, δ, is also given for distant and near vision. Unfortunately, it is not possible to indicate the precision of the data for each measurement, since this was not recorded on the data forms available. However, on the average, this was of the usual order of 0.25 percent to 0.5 percent magnification differences.

A cursory study of the data shows a reasonably close agreement between the meascomparison to the variability or reliability of data obtained on the same instrument for both visual distances.

The quantitative relation between the distant and near findings for each instrument and each meridian is the slope of the line which best describes the data in a scatterplot diagram. Such a plot is shown in Figure 3, for data of the space-eikonometer for the horizontal meridian. In this figure, the measurements found for distant vision are plotted

along the abscissa, those for near vision along the ordinate. The slope of the line (which here will be called the mean regression line) best describing the location of the points is found by the method of least squares. For these data the sum of the squares of the distance of each point from the regression line has been minimized. The values of the slopes computed for the five sets of data are given in Table 2.

Other things being equal, one might expect on the average a 1 : 1 relationship between the two findings, that is, a measurement of one percent at distant vision would correspond to a measurement of one percent at near vision. Except for the direct-comparison eikonometer in the horizontal meridian, this 1 : 1 ratio is essentially realized, as an inspection of the table will show. Perhaps there is a tendency for the data for near vision to be slightly lower than those for distant vision. For the horizontal meridian in the exception noted previously, the near-vision data are substantially greater by 37 percent.

Because of the nearly 1 : 1 ratio, the standard deviation(which is the measure of variability) of the differences between the measurements for distant and near vision is also a measure of the degree to which the near-vision aniseikonic error can be predicted by the distant vision measurements. That is, the standard deviation is the standard error of estimate of the data. On a percentage cumulative basis, 70 percent of the subjects had differences between the distant and near-vision findings less than that difference

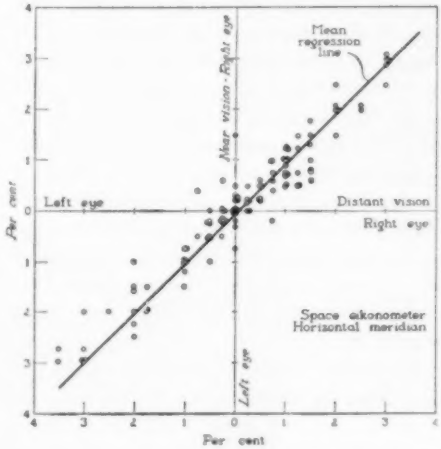

Fig. 3 (Ogle and Triller). Scatter plot of the comparative eikonometer measurements in the horizontal meridian for distant and near vision—space-eikonometer.

TABLE 2

THE SIGNIFICANT STATISTICAL QUANTITIES WHICH DESCRIBE THE RELATIONSHIP BETWEEN THE MEASUREMENTS OF ANISEIKONIC ERRORS AT DISTANT AND NEAR VISION IN THE HORIZONTAL AND VERTICAL MERIDIANS

		Direct-Comparison Eikonometer		Stereoscopic Space-Eikonometer		
		Horizontal	Vertical	Horizontal	Vertical	Declination
Slope of mean regression line:	Near / Distant	1.37	0.99	0.96	0.92	0.97
Standard deviation (n −d)		0.69%	0.54%	0.40%	0.50%	0.19°
Standard deviation for reliability	Distant	0.42%	0.36%	(0.3%)*	(0.4%)*	(0.2°)*
	Near	1.10%	0.60%	(0.5%)*	(0.5%)*	(0.3°)*
Pearson correlation coefficient		0.84	0.94	0.97	0.95	0.91
Means of data	Distant	0.06%	0.00%	−0.26%	−0.37%	+0.02°
	Near	0.91%	0.09%	−0.28%	−0.45%	+0.05°

* Estimated values.

defined as the standard deviation. The standard deviations for the five categories are given in the second row of Table 2.

The extent to which the near-vision data are correlated with those for distant vision is indicated by a comparison of the standard deviations found previously with the standard deviations of the repeatability or reliability tests of each instrument determined through repeated tests. For the direct comparison eikonometer such data exist.[2] They can at the present only be estimated for the space-eikonometer. These values are given in the third and fourth rows of Table 2. The estimated values were ascertained by a study of the stereoscopic sensitivities of subjects in the space-eikonometer under controlled conditions,[9] and of the correlation between the space-eikonometer and the direct-comparison eikonometer,[8] together with the standard deviations from the repeatability of the latter instrument.

While the Pearson correlation coefficient is difficult to interpret for the data of the type presented, it is given, also in Table 2, for what it may be worth.

A study of the table shows that, on the basis of the data available, the aniseikonic error at a near visual distance is essentially the same as that measured for distant vision, within the precision with which the measurements can be made.

One could not expect a good agreement between the findings for distant and near vision with the direct-comparison eikonometer because of the known poorer repeatability of the instrument for near vision. The means of the measurements for the near-vision test also show a marked bias. Since this did not appear with the distant-vision data nor for near vision in the vertical meridian, it probably cannot be due to an instrumental error per se. The means of the several sets of data also suggest that an error of about 0.25 percent magnification existed in the optical systems or targets of the space-eikonometer used in this experiment.

Mayo Clinic.

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ENUCLEATION AND ALLIED PROCEDURES*

PART II. A SURVEY OF SEMIBURIED IMPLANTS†

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TRANSMISSION OF MOTION OF STUMP TO PROSTHESIS WITHOUT DIRECT ATTACHMENT

As early as 1917 Dimitry[194] designed a prothesis shaped like a Snellen reform eye but with a concavity in the posterior surface designed to clasp the stump by suction. He temporarily abandoned his idea because actual motility of the stump was not imparted to the prosthesis but, in 1942, he described deliberate creation of an elevated convex stump which would project forward far enough to fit into a prothesis with a posterior concavity of 11-mm. radius, and actually obtained a patent on this prothesis,[195] but he did not report any actual results.[196]

In 1940, Cutler[197] described the use of his "basket" type implant. This procedure afforded the first uniformly successful means of moving the prosthesis along with the stump. He implanted a cup-shaped acrylic framework, 15 mm. in diameter and 11 mm. deep, into Tenon's capsule, with its concave aspect anteriorly (fig. 1).

A double-armed suture was passed through holes in the bottom of the cuplike implant, out through the edges of Tenon's capsule and conjunctiva and through holes in a 5-mm. acrylic stud, rounded on the posterior end. Tenon's capsule and conjunctiva were next overlapped and firmly united by other sutures. The initial suture was then tied tightly enough to press the stud down into the basket, thus carrying Tenon's capsule and conjunctiva against the perforated acrylic framework so that, when healing was complete, a deep concavity with fairly rigid walls remained in the center of the freely movable stump. The prosthesis used after this operation had a smooth,

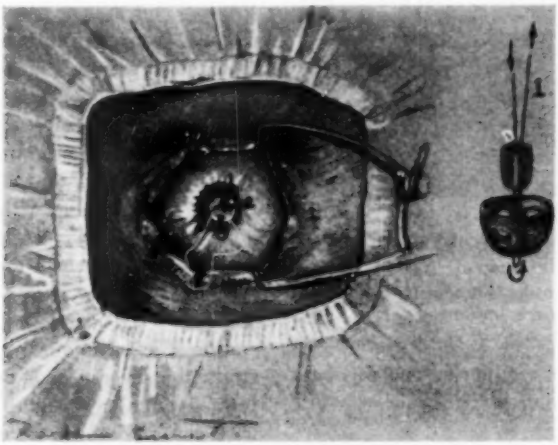

Fig. 1 (Guyton). Cutler's basket implant.

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* From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital. Candidate's thesis for membership in the American Ophthalmological Society, accepted by the Committee on Theses.

† Part I of this paper appeared in the November, 1949, issue of the JOURNAL, pages 1517-1534.

somewhat cone-shaped projection on its posterior surface which would fit into the concavity of the stump and thus acquire motility (fig. 2).

Cutler reported excellent results in 50 enucleations performed with his basket implant. This procedure was a tremendous advance over previous procedures, and it would undoubtedly have attained very widespread use had not semiburied implants been introduced very shortly afterward.

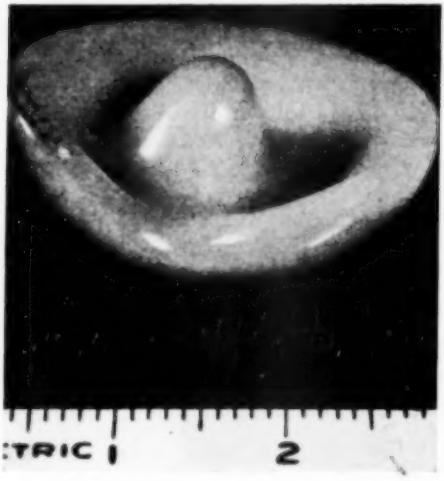

Fig. 2 (Guyton). Prosthesis used after insertion of Cutler's implant.

Semiburied implants with directly attached prostheses

Ruedemann's plastic eye implant

In 1941 Ruedemann[198] conceived the idea that a prothesis made of acrylic and shaped like a whole eyeball might serve as a permanent, nonremovable substitute for an enucleated eye if inserted into Tenon's capsule, the rectus muscles attached, and the anterior portion (shaped and colored to match the fellow eye) left exposed. The possibility of a nonviable structure with direct attachment to living, subepithelial tissue remaining permanently partially buried and partially exposed, with a consequent line of transition between epithelium and subepithelial tissue in the lining of the structure, is a natural occurrence in the case of teeth; nevertheless, Ruedemann's application of this principle to prostheses was completely original not only in the field of ophthalmology, but in surgery as a whole.

Ruedemann began implanting whole acrylic eyes into Tenon's capsule in 1941, and, in 1945, he first reported this procedure[1] before the American Ophthalmological Society. He had by that time performed over 100 such implantations. When he first began performing this operation, he used various sized and shaped eyes, "mostly wrong," and attached the eye in place with various suture materials and techniques, "also mostly wrong." However, by "trial and error plus much effort" he obtained more and more successful results, and implanted artificial eyes exhibiting normal motility and without retraction of the upper lid sulcus. He also had successes with delayed implantations into deformed sockets, using fibrous tissue for attachment if the recti could not be identified.

When Ruedemann first reported his operation, the technique he preferred was to attach the severed ends of the recti to perforated tantalum paddles by fine tantalum wire sutures, which were then attached to the plastic eye (figs. 3 and 4). The plastic eye matched the fellow eye in coloring and size. He listed the following complications: dyes fading, muscles coming loose, conjunctival discharge if conjunctiva retracted so as to expose tantalum suture or paddle, strabismus and ptosis if the eye was set too deeply in the orbit.

In May, 1945, Dr. Alan Woods visited Dr. Ruedemann in Cleveland and watched him implant two of his plastic eyes, and also examined a number of patients who had already undergone such an operation. Dr. Woods was so impressed he obtained Dr.

Ruedemann's permission to utilize this procedure, and he inserted the first of these implants at the Wilmer Institute in June, 1945. Between June, 1945, and December, 1945, 10 of the Reudemann implants were inserted. Nine were used at the time of enucleation and one after removal of a displaced gold-ball implant. The initial results were excellent in four of these patients, there was appreciable tropia in five, with some persistent ptosis in three. In the remaining patient insertion of too large an implant resulted in immobility of the eye. One patient developed orbital cellulitis three months after an initially successful operation.

Nine of the implants were extruded at intervals of seven days to 22 months following operation, the average period between operation and extrusion being 10 months. These extrusions apparently resulted from contracture of the fairly dense fibrous sheaths around the buried portions of the implants and from retraction of the conjunctiva from the ends of the rectus muscles which eventually, despite repair, broke free from their attachments to the tantalum clips. One implant was still in place 29 months after operation, but there was some exposure of the paddles and attached muscle ends.

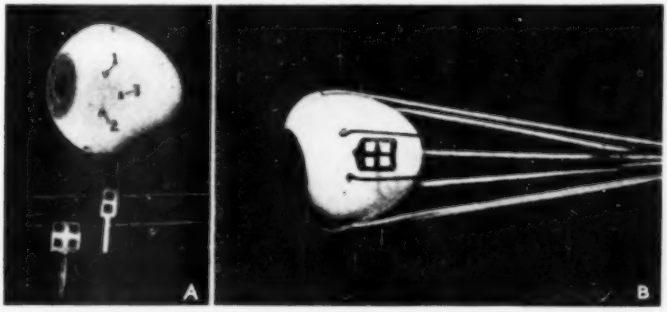

Fig. 3 (Guyton). Ruedemann's original plastic eye implant.

In a recent personal communication,[198] Ruedemann stated that every one of the

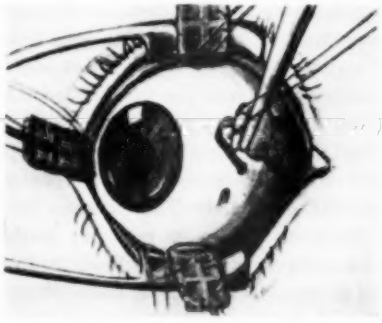

Fig. 4 (Guyton). Attachment of muscles to Ruedemann's whole acrylic eye via tantalum paddles.

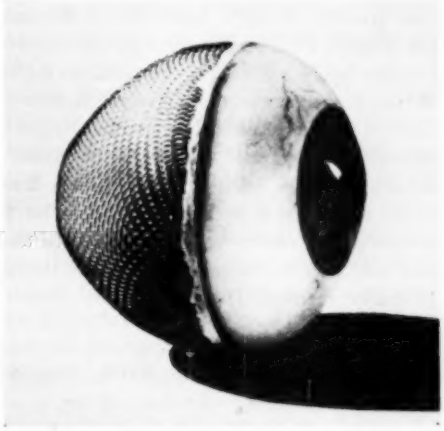

Fig. 5 (Guyton). Ruedemann's modified acrylic eye implant, with tantalum mesh for attachment of tissues.

plastic eyes he had implanted with muscles connected to tantalum clips was eventually extruded or had to be removed. Nevertheless, the eyes stayed in place long enough to suggest that improved techniques might result in permanently successful implantations.

As early as November, 1945, Ruedemann proposed utilizing a whole eye implant with tantalum mesh surrounding the buried portion,[199] and soon thereafter he began implanting such eyes (fig. 5).

The rectus muscles and the edge of Tenon's capsule were simply sutured to the anterior border of the mesh, with the sutures also passing through holes drilled through the plastic. Tenon's capsule and the muscles became firmly adherent to the tantalum mesh. When it was necessary to straighten the eye after it was implanted, Ruedemann found it difficult to separate muscles and Tenon's capsule from the mesh-work, but he has done so by means of a periosteal elevator. Since adopting this never type of implant, he has had only a few extrusions, which he thinks probably resulted from using too large a size.

Cutler's ring implant with attachable prosthesis

In October, 1945, Cutler began inserting buried implants to which protheses could be coupled after the socket had healed. He described the first implant of this type (January, 1947) as "a positive contact ball and ring implant."[2] This ring implant consisted of an acrylic sphere with a short anterior cylindrical prolongation surrounded by a gold or vitallium ring attached to the plastic by four equidistant metal bars, and with a metal cup inset in its anterior surface (fig. 6). The ring implant was inserted following simple enucleation by folding the ends of the recti around the ring from within outward, folding Tenon's capsule and conjunctiva over the ring in the opposite direction, and suturing these structures firmly in position with nonabsorbable sutures (fig. 7).

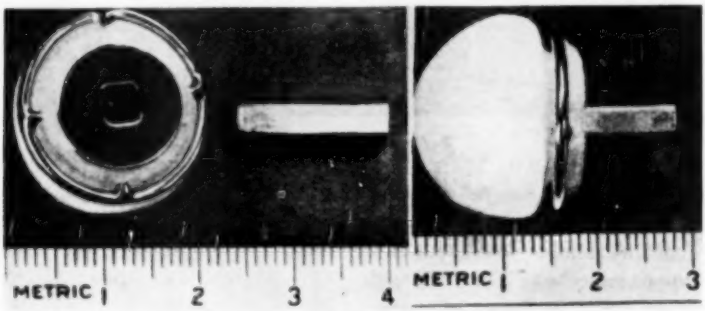

Fig. 6 (Guyton). Cutler's ring implant.

After the socket was completely healed, a prosthesis was made to match the visible anterior segment of the other eye in size and color. This prosthesis was similar to acrylic prostheses worn after simple enucleation except that the scleral portion was smaller and more curved, so as not to extend into the fornices. A metal pin which fitted snugly into the cup of the implant was attached to the back of the prosthesis, the pin being positioned on the prosthesis so that the eyes were in perfect alignment. The pressure of the lids held the pin in its cup and produced firm attachment of the prosthesis to the implant so that full motility of the implant was conveyed to the prosthesis.

The use of this male-female coupling eliminated the necessity of inserting a whole

eye implant, which had to be individually made prior to operation and therefore could not be used for emergency enucleations. The coupling permitted construction and adjustment of the prosthesis after healing occurred, insured perfect alignment and position, and allowed for replacement of prostheses if they became faded, scratched, or otherwise imperfect. Cutler's introduction of this two-piece principle was a notable step in the attainment of uniform final results.

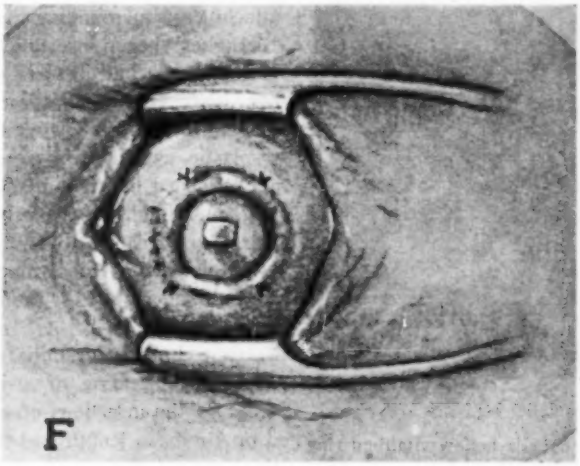

Fig. 7 (Guyton). Cutler's ring implant sutured in position.

Cutler reported the use of his ring implant in 22 patients. Five implants had to be removed. Three of these were the first he had used and were constructed of three pieces screwed together; in one case the patient developed orbital cellulitis and pneumonia six months after the implant was inserted; in the other two cases, the ring became exposed by erosion through its covering of Tenon's capsule and conjunctiva, and this led to a gradual increase in the exposure of the ring and the eventual detachment of the muscles. Cutler noted that attempts to repair the covering of a partially exposed ring were fruitless.

In the group of cases originally reported by Cutler the follow-up was limited to only a few months. In a recent personal communication, Cutler[200] stated he was gathering follow-up statistics but that these were not yet complete. "The longest follow-up I have a record of is 2½ years; incidentally this patient has not had his prosthesis out during the past year and a half. None of my original implants put in since April, 1946, have come out. I haven't done many secondary operations. However, I think one half have come out for various reasons and the other half are doing very well."

In June, 1946, O'Brien, Allen, and Allen[201] reported having inserted a few implants like those of Cutler into Tenon's capsule. They modified Cutler's original design slightly by substituting bridges across grooves for the ring. The recti were split after passing under the bridges and sutured together around the anterior peg rather than folded back on themselves. The few implants inserted during the six months preceding their report gave encouraging results. However, in a recent personal communication about semiburied implants, O'Brien[202] said, "I did make a preliminary report in San Francisco several years ago but I am not as enthusiastic

as I was at that time. It seems to me there remains a great deal to do before these things are satisfactory."

At the Wilmer Institute, 23 Cutler ring implants were inserted between March, 1946, and March, 1947. Two of these were reimplantations, one at the time a Ruedemann whole eye implant was extruded, and the other 15 days after extrusion of a previous ring implant. Both of these reimplantations were extruded within four months. Of the 21 ring implants inserted at the time of enucleation, seven were still in place and gave excellent cosmetic results after follow-up periods of 1 to 11 months (average five months). Fourteen were extruded at intervals of one day to 11 months (average five months) after insertion.

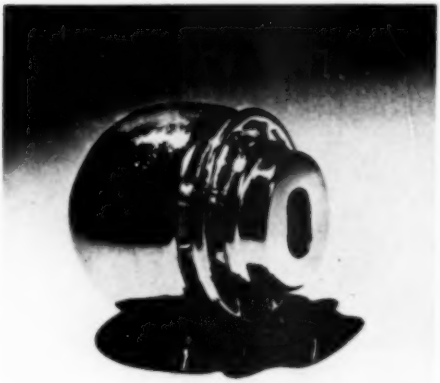

Fig. 8 (Guyton). Hughes's hollow vitallium ring implant.

The events leading to extrusion were exactly the same as those originally noted by Cutler: exposure of a small segment of ring, usually in its upper portion, and gradual extension of this defect, with eventual detachment of the muscles. We likewise found, as had Cutler, that attempts to repair a defect over the ring were uniformly unsuccessful. However, in all fairness to the ring implant, it must be recorded that these operations were performed by a number of different surgeons, who in some instances did not follow the exact technique of suturing advocated by Cutler, and that the implants we used had slightly less space between the ring and body of the implant than Cutler believed desirable. Also, the attachable prostheses used with the first implants were too flat and too large, so that attempted maximal rotation resulted in a strain on the attachments surrounding the ring.

Hughes[49] began inserting slightly modified ring implants into Tenon's capsule in October, 1946. His modification consisted of an implant made of hollow vitallium rather than of plastic, with the ring closer to the implant and attached by eight bars instead of four (fig. 8). The diameter of the buried portion was approximately 18 mm. if it was to be used immediately following enucleation, and 12 mm. if designed for the replacement of a buried implant.

His technique for initial implantation included preservation of strips of sclera in front of the insertions of each of the recti, 3 or 4 mm. in length and two thirds of the thickness of the sclera, thus extending the length of the rectus tendons so they would be sufficiently long to pass around the attachment ring without being under tension. For replacement of a buried implant, Hughes thought the ring implant feasible only if the buried implant was approximately in normal location with good motility and with enough connective tissue attached to the recti to fold over the ring and permit adequate attachment. Initial good results were obtained in the four cases described in his preliminary report, but all four operations had been performed within the preceding four months. In a recent personal communication, Hughes[203] cited some nice results with the late replacement implants, as well as with those inserted at the time of enucleation.

Cusick[204] has inserted 10 Cutler ring implants (nine primary and one secondary)

since October, 1946. The first one he inserted was extruded following gradual exposure of the upper portion of the ring after about two months. In his subsequent operations, he paid considerable attention to overlapping the upper structures more extensively than the lower ones, thus providing a relatively thicker covering for the upper portion of the ring, and he has had no more extrusions. He is probably correct in believing this manuever was responsible for his subsequent good results. Cooper[205] has had no extrusions of three ring implantations six months after the operations.

Rosen[206] has recently described as original an implant having the same slight modification which O'Brien, Allen, and Allen, first reported in June, 1946.

The present status of Cutler's ring implant may be summarized as follows: It is the first semiburied implant with a detachable prosthesis, and represents a distinct advance in enucleation procedures. Furthermore, if the ring implant is properly made and is inserted with careful technique and with wide overlapping of Tenon's capsule (especially above), the cosmetic results are not only initially excellent, but will probably be permanent in a majority of cases. This implant is seldom suitable for delayed implantations.

O'Brien's semiburied evisceration implant with attachable prosthesis

In the June, 1946, report of O'Brien, Allen, and Allen[201] already cited, the authors also described use of a few semiburied intrascleral implants, which they originated. The first of these gave excellent initial results but became gradually extruded. A change in the size of the implants and in the technique of insertion was made after the first few extrusions, and the implants they then inserted seemed less likely to extrude.

The implant in use at the time of their report consisted of an acrylic ellipsoid, 11.7 by 14 mm., with a short cylindrical peg 4 mm. in diameter extending forward from its anterior surface, and a plastic flange which could be fastened around this peg after the implant was inserted. The anterior surface of the peg was inset with a round cup for the reception of the pin of the attachable prosthesis. To insert this implant, a 4-mm. hole was trephined through the center of the cornea, a meridional incision 18 to 20 mm. long was made through the upper temporal sclera, the contents of the globe were eviscerated, the implant was inserted so that the peg protruded through the hole in the cornea, the scleral incision was closed and the flange around the peg fastened to prevent its slipping back through the cornea. No long-term results were available at the time of the preliminary report, and O'Brien[202] is not now as enthusiastic about these implants as he was in 1946.

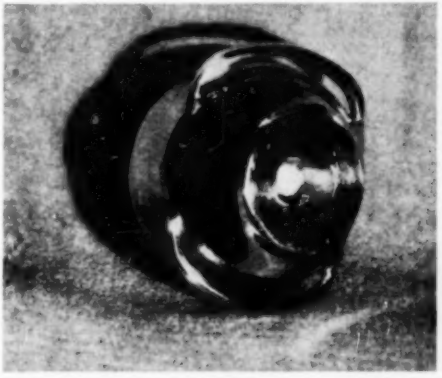

Fig. 9 (Guyton). Hughes's hollow vitallium evisceration implant.

Hughes[49] began using evisceration implants resembling those of O'Brien, Allen, and Allen as well as ring implants in October, 1946. His evisceration implants were made of hollow vitallium, and his later models had two small bridges through which strips of sclera could be passed for firmer attachment (fig. 9). His technique involved removal of the entire cornea. A preliminary report included four cases of evisceration with these semiburied implants. Two of the

implants were extruded within the short follow-up period, and a third case had to be reoperated. In a recent communication Hughes[203] said that he made some changes in the design of the implant, using two different sizes, and that he is now carrying out further investigations in this line.

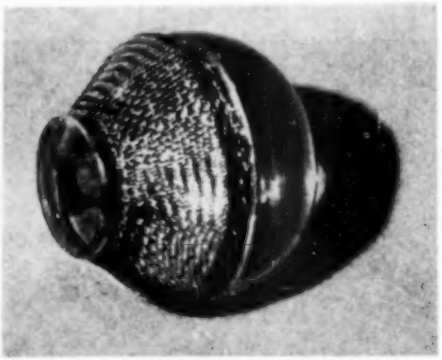

Fig. 10 (Guyton). Whitney and Olson's acrylic implant with tantalum mesh belt for attachment of recti and Tenon's capsule.

In summary, it may be fairly concluded that this type of evisceration implant has thus far proved disappointing.

Semiburied acrylic implants partially covered with tantalum mesh

In August, 1946, Whitney and Olson[5] first inserted a semiburied implant partially surrounded with tantalum mesh and adapted for an attachable prosthesis. This first implant was an acrylic ellipsoid, 18 by 20 mm., covered except over the slightly protruding anterior face by fine tantalum mesh (fig. 10).

After two of these implants had been inserted, Whitney and Olson decided that better motility would result if the posterior surface of the implant were left smooth and the sides of the implant covered with mesh.

This decision was based on the observation of two sockets in which buried doughnut-shaped implants of fine tantalum wire had been inserted the previous year: the stumps were initially freely movable, but after some months the motility gradually diminished, the position of the stumps apparently becoming "fixed" by extensive fibrosis.

One implant with a smooth posterior surface was inserted in October, 1946. Between September, 1947, and March, 1948, they inserted 10 additional implants which differed only in having a narrower rim of tantalum mesh, a groove around the anterior portion of the implant beneath the mesh, and a larger, shallower cup to serve as the female coupling (the small, deep cup first used had collected an odoriferous discharge). All of these implants were inserted at the time of enucleation. Thus far none have extruded, and the results have been excellent. The only complaints Whitney and Olson make are that some sockets have had more discharge than after simple enucleation, and that in some cases there is actual hypermotility of the prostheses.

In March, 1947, Stone[207] began insertion of implants (fig. 11) almost exactly like those of Whitney and Olson, and in October, 1947, he reviewed the results of 20 initial

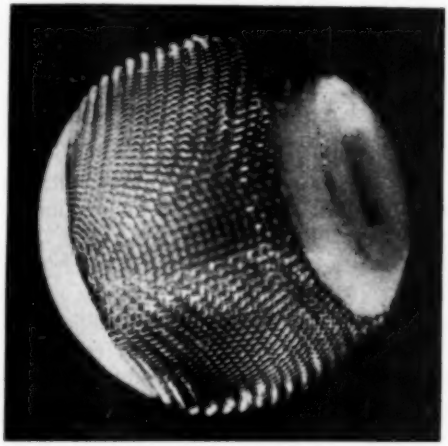

Fig. 11 (Guyton). Stone's acrylic and tantalum mesh implant.

implantations and four delayed implantations. There were no extrusions, and the motility of the implants varied from 50 to 100 percent of normal. The only complications were conjunctivitis in three cases.

In a recent communication, Stone[208] noted that there were as yet no extrusions. In two cases where reoperation was performed to obtain better motion from individual muscles he found "the fibroblastic proliferation of Tenon's capsule and the retrobulbar fat was so firm that it was impossible to separate it from the meshwork with a spatula. It was also so coarse that cutting with scissors was difficult. The conjunctival epithelium had firmly engaged itself at the anterior edge of the meshwork and it was also impossible to separate this junction with a spatula."

Since May, 1947, Cutler[200] has used an implant (fig. 12) similar to that of Whitney and Olson, in preference to his original ring implant. He terms this newer implant the "universal type," for use in enucleations, reimplantations, and his enucleo-evisceration operation (preservation of a scleral ring containing the attachments of the rectus muscles). He says "about 25 or 30 have been used since May, 1947, in Wilmington. One secondary came out after about five days in the hospital because I discontinued the pressure dressing in a patient who had a hemorrhage. I didn't think it *could* come out—but it did. The Gougelman Company up to 2 or 3 weeks ago, had sold, I believe, about 150 of these. No expulsions are known to them. . . . The use of the mesh implant is short and simple. Catgut sutures only are used." (Whitney and Olson, and also Stone, prefer sutures of fine tantalum wire.) Cutler has found the range of movement with this type of implant is approximately the same as that with his original ring implant.

In summary, this Whitney-Olson type of semiburied implant appears to be better than any of those previously described. A considerable number have been implanted during the past 12 months with consistently excellent results. However, it is well to remember that, with this as well as with other semiburied implants, "the theoretical disadvantage of the procedure is great. It controverts basic surgical dictum that a wound must be completely epithelized in order not to break down. Not only is the wound seemingly not epithelized, but there has also been introduced a foreign body which is not epithelized. When an analogous procedure has been attempted in the past by dental or orthopedic surgeons, no matter how small their unepithelized pin might be, sloughing invaribly has ensued."[207]

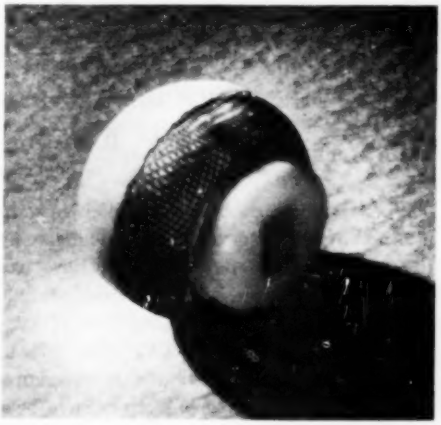

Fig. 12 (Guyton). Cutler's "universal" acrylic and tantalum mesh implant.

It seems probable that the excellent results so far obtained with tantalum-mesh attached implants will be permanent; but only long-term follow-ups can eliminate the possibilities of gradual late restriction of motility because of too heavy proliferation of fibrous tissue around the implants (such as noted by Whitney and Olson with buried implants of tantalum wire) or of late orbital infections occurring because of lack of epithelialization around the implant.

(To be concluded.)

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THE NONSURGICAL TREATMENT OF HETEROTROPIA*

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Saint Louis, Missouri

There are three objectives which may be attained by nonsurgical therapeutic means in the patient with heterotropia. They are: (1) The destruction of abnormal retinal correspondence, (2) the abolition of suppression amblyopia, and (3) some adjustment of the accommodation-convergence reflex. When these three objectives have been reached, the final goal in the treatment of all patients with heterotropia—fusion—may often be obtained in a surprising number of cases. The three objectives will be considered in the order mentioned.

ABNORMAL RETINAL CORRESPONDENCE

Corresponding retinal elements are those which have the same visual direction. In the person whose eyes are normal and who has normal retinal correspondence, imagine some object, O, located straight ahead as the object of gaze. The image of O will fall on corresponding retinal points in the two eyes. Any object whose image falls at A in the right eye will be projected back into space to the point O and the same will be true of the point B in the left eye. Since A and B have the same visual direction, they are said

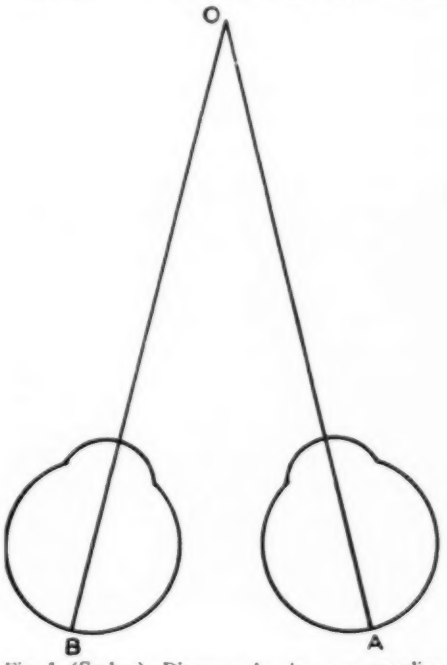

Fig. 1 (Scobee). Diagram showing corresponding retinal points.

* From the Department of Ophthalmology, Washington University School of Medicine, and the Oscar Johnson Institute. This is part of a study made under contract with the Office of Naval Research as Project N6onr-202, Task Order I. Read before the Kansas City Southwest Clinical Society, Kansas City, October 7, 1948.

to be corresponding retinal points. This is shown in Figure 1.

A person with esotropia, for example, has an entirely different situation, as shown in Figure 2. O is again the object of gaze of the right eye and the image of O falls at A; the left eye, however, is turned inward in esotropia and the image of O falls not on B but on the point Z.

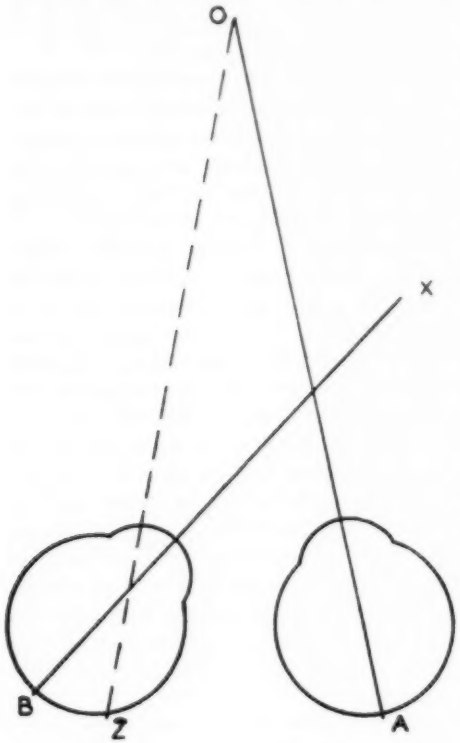

Fig. 2 (Scobee). Diagram showing abnormal retinal correspondence (esotropia).

In Figure 1, A and B, representing the two foveas, are seen to be corresponding points. In Figure 2, O is forming an image at A and at Z; A and Z are obviously not corresponding points because any object imaged at A will be interpreted as being straight ahead while any object imaged at Z will normally be interpreted as being located to the left of the midline.

Since the patient has esotropia, however, every time he looks at the object O, it is imaged at A in the right eye and at Z in the left eye. After countless repetitions of this situation, the patient finally learns to interpret images falling at Z as being straight ahead instead of to the left! A and Z have now become corresponding retinal points in that they have the same visual direction. A and B are normally corresponding retinal points and yet A and Z have developed an abnormal relationship of correspondence and the patient is said to have abnormal retinal correspondence.

The therapeutic problem in such a case is obviously first to destroy the abnormal relationship between A and Z and, secondly, to reëstablish the proper relationship between A and B.

Abnormal retinal correspondence is a conditioned reflex which has developed in response to a conditioning stimulus. Every time the patient looks at any object with the point A of his right eye, the point Z in the left eye is also stimulated and the relationship between A and Z is strengthened. If one would destroy a conditioned reflex, one must completely remove the conditioning stimulus. If the fixation of the objects with the right eye (actually, with the point A of the right eye) is the conditioning stimulus and the conditioning stimulus must be removed, then the fixation of objects with the point A of the right eye must be prevented at all costs. In other words, the right eye must be constantly occluded and thus prevented from fixing on any object at all.

Once the right eye is prevented by occlusion from assuming fixation, the left eye is forced to take up the task. The spot of greatest potential retinal sensitivity in the left eye is B, its fovea, even though it has not been used because of the abnormal position of the left eye in esotropia; the point Z in the left eye has been used in this instance as a matter of necessity. Once it is no longer necessary to use Z, the left eye will prefer to use the point B because B is

far more sensitive, potentially, than is Z. When Z is no longer used in conjunction with A, the abnormal relationship between these two abnormally corresponding points begins to weaken and will eventually disappear in most cases. Meanwhile, B—the normally corresponding point of A—is being used continuously. After the abnormal relationship between A and Z has been destroyed, the patient is free to develop a normal relationship between A and B provided the eyes can be held in such a position that this is possible.

While the foregoing paragraphs are somewhat of an oversimplification of the actual situation, nevertheless the idea as a whole is sound and should serve to clarify the problem. There is no question but that complete and constant occlusion of the nondeviating eye in the patient with heterotropia is the first and most important step in the destruction of abnormal retinal correspondence.

Suppression amblyopia

This may be defined as the apparent loss of vision in the crossing eye which develops in patients with monocular heterotropia. In the past, this visual loss has been somewhat erroneously called amblyopia ex anopsia or the blindness of disuse. In the first place, the visual loss is not a blindness of disuse because it does not occur in the retina itself but instead is localized at the level of the occipital visual cortex and is believed to occur as a result of active suppression in that area.

Suppression amblyopia occurs as the result of a conditioned reflex in the same way that abnormal retinal correspondence develops. It would not be incorrect to think of the two as developing simultaneously. To return to Figure 2, the patient is fixing an object O with the point A of the right eye; the deviating left eye has the point B (the normally corresponding point with A) aimed at some other object, X.

If the patient is to keep from seeing X and O superimposed at the same point in space—an impression which would obviously be very confusing—then the image falling either at A or at B must be ignored by the brain. The image falling at B, that is, the image falling at the fovea of the deviating or crossing eye, is the one which is invariably ignored and it is more than a passive inattention toward images falling at B; it is an actual suppression which is active and certainly not passive.

One cannot merely ignore a stick of dynamite with a lighted fuse lying nearby if one expects to continue in the efficient performance of the daily tasks of living; the fuse must be extinguished—in short, something active must be done about the situation.

The brain in actively ignoring images falling at B is "doing something" about the situation. Every time the patient looks at an object, such as O, with the point A of the right eye, the brain must ignore whatever object (such as X) that may happen to cast its image at B in the crossing left eye.

Thus, the stimulus for suppression in the brain connected with the point B in the left eye is the use of the point A in the right eye for fixation. Each time the patient looks at an object with A in the right eye, the point B in the crossing eye must be suppressed a little bit more. Suppression amblyopia is a conditioned reflex and the conditioning stimulus is the use of the point A in the nondeviating eye.

It has already been shown that the use of this same point A in the nondeviating eye is also the stimulus for the development of another conditioned reflex—that of abnormal retinal correspondence. As in this former instance, the treatment of suppression amblyopia is the destruction of the conditioned reflex which is responsible for its existence. This means removal of the conditioning stimulus.

The conditioning stimulus is easily eliminated by merely occluding the right eye and thus preventing the stimulation of the point A. This procedure forces the use of the left eye and its area of potentially greatest sensi-

tivity, the point B. With A out of the picture, there is no longer any need for the brain to ignore B but instead there is an actual demand for the recognition of objects falling at B. Thus may suppression amblyopia, a conditioned reflex, be destroyed by removing the conditioning stimulus, the latter being accomplished by occluding the habitually fixing eye.

It may now be appreciated that occlusion of the nondeviating eye in the patient with monocular heterotropia accomplishes two purposes simultaneously: (1) The disruption of abnormal retinal correspondence, and (2) the destruction of suppression amblyopia. In both instances, we have a conditioned reflex which is abolished by removal of the conditioning stimulus. In each case, the conditioning stimulus is the fixation of objects by the noncrossing eye. If a conditioned reflex is to be thoroughly abolished, the conditioning stimulus must be completely removed. This calls for constant and complete occlusion of the good or habitually fixing eye until both goals have been attained.

It is to be emphasized that wearing a patch over the habitually fixing eye for a few hours a day is not constant occlusion and is almost worthless. A conditioned reflex is extremely difficult to destroy if the conditioning stimulus is removed for only a few hours a day and is then allowed to act during the rest of the waking hours.

Atropinization of the better seeing eye instead of occlusion of that eye is of little value; the patient will continue to use the atropinized eye for distant fixation and use the poorer eye only for near objects.

A minimum trial period of six months of constant and complete occlusion should be insisted upon in every case. If the occlusion has been faithfully carried out and there is no improvement in vision at the end of this period, the occlusion may be discontinued and a tentative diagnosis made of congenital ambylopia.

Of the various types of occluders available on the market, the most satisfactory is the flesh-colored elastoplast patch. It is impossible for the patient to "peep" with this type of occlusion.

The patient with the better eye occluded should be encouraged to look at large, colored picture books, to play with large, brightly colored toys, especially large balls. The cheiroscope is an ingenious and useful instrument in stimulating the use of the poorer eye. Ruedemann has suggested the use of a kaleidoscope in these patients and the idea works well in practice; it is particularly important that the toy be held aimed at a sufficiently bright light source in order that the rapidly changing pictures may be properly illuminated.

Adjusting the accommodation-convergence reflex

All of the remaining nonsurgical therapeutic measures in heterotropia may be gathered into this general classification. Included are the use of glasses, prolonged atropinization, prohibition of close work, certain forms of orthoptics, and more recently, the use of pilocarpine, eserine, and even of D.F.P. They will be discussed in the order named.

1. Glasses. Correction of any existing ametropia is the first step and an important part in the therapy of heterotropia because the majority of cases have an accommodative element, no matter how small. Because hypermetropia leads to compensatory accommodation and an associated excessive convergence, any hypermetropia found in patients with esotropia should be fully corrected; if exotropia is present and there is hypermetropia, only the minimum correction needed to secure clear vision is advisable. When myopia is present and there is esotropia, only the minimum correction needed to secure clear vision should be given; on the other hand, if there is exotropia and myopia, a very full or even a mild overcorrection of the myopia is indicated. Astigmatism, irrespective of type, should always be fully corrected, regardless of

whether the lateral deviation is one of esotropia or exotropia.

A word about what is meant by a "full" correction is necessary. A full correction means the entire refractive error as found under atropine cycloplegia. If a patient has esotropia and is found to have 4.25 diopters of hypermetropia, the full 4.25 diopters should be given in the prescription, deducting nothing for ciliary tone.

It is rare that one obtains complete cycloplegia in a child, even with atropine, and hence what appears to be a full correction is usually an actual undercorrection by an amount equal to the incompleteness of the cycloplegia. The deduction of even 0.5D. from the atropine findings will sometimes make a difference of as much as 10 degrees in the amount of deviation corrected by glasses.

We have discontinued entirely the use of atropine as an eyedrop in children and even adults with heterotropia for two reasons: (1) The cycloplegia is often incomplete because either tears quickly flush much of the drop from the sac or dilute it to a point where it is relatively ineffective, and (2) systemic reactions are frequently encountered in children.

In place of the atropine drop, atropine ophthalmic ointment (0.5 or 1 percent) is routinely used. Systemic reactions with the ointment are very rare and the ointment results in a higher concentration of atropine in the sac over a longer period of time, thus leading to much better cycloplegia.

If a parent has difficulty in getting any medicine into the child patient's eyes, the ointment is superior to the drop because even though it only gets on the lashes, it soon melts and runs into the eyes. The ointment is used three times daily for a minimum of three days prior to refraction.

A full correction is prescribed, no matter how small the error that is found, and the glasses are then worn constantly for a minimum of one month before any judgement of their effect in reducing the deviation is attempted. The one-month interval is absolutely essential in order that the patient may establish a new accommodation-convergence ratio.

The routine just described often seems to work a hardship on the out-of-town patient and many oculists are wont to skip it in such instances. Their final results are proportionately bad. While such patients may at first seem to object, their final reaction is invariably one of satisfaction, the thought seemingly uppermost in their minds being that the doctor was thorough.

The occasional child who complains of blurred vision with his full correction will need to be atropinized by the use of the ointment once or twice daily for about two weeks.

A not uncommon occurrence is met with in patients whose esotropia is fairly well controlled by correcting lenses. They may suddenly seem to develop more esotropia in spite of the glasses. This is almost invariably an indication that the glasses need changing. These patients will be found to have outgrown a certain portion of their hypermetropia and a reduction in the amount of the plus sphere in their correction will, paradoxically enough, produce a corresponding reduction in the amount of esotropia.

The paradox is easily explained, however, when one recalls that a hypermetropic eye that is overcorrected—as is one that has outgrown some of its hypermetropia when the glasses are not changed—is an eye with blurred vision. The response to blurred vision is always an attempt to further accommodation with its associated convergence. Hence when vision blurs, the patient attempts to accommodate more in order to clear it and incidentally converges more in the process, thus increasing the esotropia.

Reducing the plus correction to the proper amount results in a return of clear vision and a decrease in the efforts at accommodation and incidental convergence.

2. Atropinization. Children with esotropia or marked esophoria will frequently be bene-

fited by from 3 to 6 weeks of atropinization during and immediately following systemic illnesses. The reason is obvious. The tonus of the bodily musculature as a whole is below par and the ciliary muscle is included. Excessive accommodative demands are needed in order to perform close work and excessive convergence automatically ensues.

Atropinization is also of value in high-strung children with esotropia normally corrected by glasses when they are undergoing periods of stress or strain, such as beginning school. Guibor advocates phenobarbital in small doses in such cases and it may indeed be of value in quieting a hypertonic convergence center associated with a tense central nervous system.

3. Prohibition of close work. The intelligent and high-strung child with esotropia will show an apparent increase of that esotropia during periods of stress. When this occurs, it is wise to prohibit all close work for a month, two months, or even three months. The goal of such prohibition is, of course, prevention of use of the eyes as much as possible during periods of actual esotropia and thus preventing both suppression and abnormal correspondence from developing. A child that is just on the borderline of fusion—fusing at times and at other times lapsing into tropia—should be prohibited from casual close work and confined to supervised orthoptics.

4. Orthoptics. Certain forms of orthoptics are aimed at adjusting the accommodation-convergence reflex. The goal is usually an attempt at at least a partial dissociation of accommodation and convergence. It is not within the scope of this paper to present the means by which this may be accomplished but it can be done successfully in many instances with gratifying results.

5. Pilocarpine, eserine, and D.F.P. Abraham* reports a series of cases whose treatment was based on an ingenious theory. He used miotics in patients with intermittent esotropia and reported good results in a surprisingly high percentage of such cases. He reasoned that miotics produced ciliary spasm which he chose to call "peripheral accomodative spasm" (as opposed to central accommodative spasm such as might occur in hypermetropia in response to a demand for clear images by the brain).

If such accommodation were produced artificially and peripherally, then there should be no demands centrally for accommodation and hence no associated convergence. Thus did Abraham explain the apparent beneficial effects of miotics in patients with intermittent esotropia. Attempts at confirmation of his work are not yet completed. The idea is a fascinating one for speculation, however.

Summary

The nonsurgical measures in the therapy of heterotropia have been considered. Although approximately 60 to 70 percent of all patients with heterotropia require surgery before a final cure may be effected, still the remainder may be cured by nonsurgical measures properly employed. Many of the nonsurgical measures enumerated are important prerequisites of surgery in any event and it is well for the ophthalmologist who would treat patients with heterotropia to be fully cognizant of them all.

640 South Kingshighway (10).

* Abraham, S. V.: The use of miotics in the treatment of convergent strabismus and anisometropia. Am. J. Ophth., **32**:233, 1949.

NOTES, CASES, INSTRUMENTS

VITREOUS LESIONS OBSERVED IN BOECK'S SARCOID*

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Binghamton, New York

The purpose of this report is to describe vitreous lesions found in five eyes in a series of 13 patients having sarcoidosis who were observed at the Veterans Administration Hospital at Fort Howard, Maryland, during a two-year period ending July 1, 1948. A complete study from the ophthalmic viewpoint of the cases of sarcoidosis from this hospital, including the results of nitrogen-mustard therapy in selected cases, will be submitted at a later date.

Sarcoidosis, or the Besnier-Boeck-Schaumann disease, was estimated by Woods and Guyton[2] to constitute 2 to 3 percent of cases of endogenous uveitis. Longcope,[3, 4] Fisher[4, 5] and Michelson[6] have described the general features of the disease, and Walsh[7, 8] pointed out the relationship of sarcoidosis to Heerfordt's syndrome.

With the increasing recognition of sarcoidosis by clinicians in various fields, granulomatous uveitis and the other less common ocular manifestations are assuming a greater importance as links in the chain of diagnosis, and the severely damaged eyes, which may be almost the sole residual effect of the disease, pose a difficult problem to the ophthalmologist.

The vitreous lesions consist of discrete grayish-white bodies occurring in the most dependent portion. They vary in size from dots to approximately one third of a normal disc diameter and are, for the most part, spherical. Frequently these bodies occur in chains like an isolated segment of a string of pearls. A few tubular forms have been noted, and occasionally other nondescript shapes. They may be seen with the ophthalmoscope focused on the retina, and focused in front of the retina up to a plus-10 reading. In all cases, they have been at least several disc diameters below the posterior pole, and are most numerous around the 6-o'clock position at the periphery. The bodies cast shadows from the ophthalmoscope light on the retina and the apparent distance of the bodies from their shadows indicates their relative position in the vitreous. It is almost impossible to see the lesions without fully dilating the pupil.

The patients studied were a group of 10 Negroes, two white men, and one American Indian. These veterans ranged in age from 21 to 35 years and all had generalized sarcoidosis including pulmonary lesions. All but one had peripheral node involvement. The various other sites included skin, lacrimal gland, epididymis, nasal mucosa, bone, and kidney. All diagnoses had been confirmed by one or more biopsies prior to examination by the ophthalmic department. Of the group of 13 patients, eight had eye involvement of some degree.

The three patients in whom the five eyes showed the vitreous lesions were young Negroes. All had chronic granulomatous uveitis characterized by greasy keratic precipitates on the posterior cornea, a positive aqueous flare, Koeppe and Busacca nodules, and a tendency to posterior synechia. The second eye of the third patient had a dense posterior synechia at the 6-o'clock position

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* Published with permission of the chief medical director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author. This group of patients was examined and followed as a part of a study of the effect of nitrogen mustard on sarcoidosis which, with the approval of the National Research Council, was initiated by Dr. George E. Snider, and the preliminary report was made by him in January, 1948.[1]

† Resident in Ophthalmology, Veterans Administration Hospital, Fort Howard, Maryland.

which made it impossible to visualize the area in which the vitreous bodies might be expected.

The vitreous lesions have been observed only in the eyes of patients having relatively benign eye involvement. It is possible that the incidence of lesions in this group may be higher than has been indicated because, in the more severely involved eyes, it has been impossible to see the area in which they are to be found. Over a period of three months, there has been no marked change in the size, number, or character of the vitreous bodies in the five eyes, although in all cases the uveitis has become quiescent.

The present approach to the pathology of the vitreous lesions is necessarily indirect because all five eyes have useful vision. The area in which they are found suggests that they are of a higher specific gravity than the vitreous. The patient having the largest number of lesions was placed in a Trendelenburg position for three hours, and all patients were observed after periods of recumbency to check for drift of the bodies. However, no demonstrable change in their position was noted. It seems, therefore, that the specific gravity of the vitreous bodies must be essentially the same as that of the vitreous.

Two hypotheses as to the nature of these bodies have been considered; that they are similar in nature to Koeppe or Busacca nodules of the iris, which are collections of cells of the lymphoid series, and, that they are serous exudates which have been formed by an inflamed ciliary body and are therefore largely protein in composition. Up to the present, it has not been possible to prove or disprove either hypothesis.

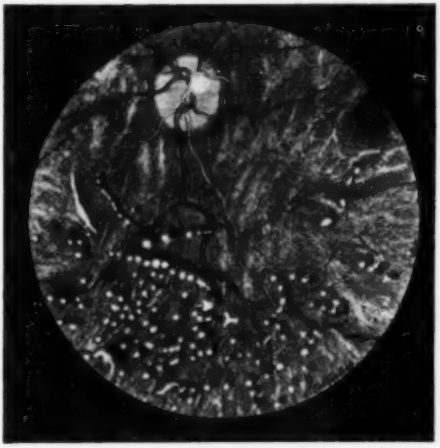

Fig. 1 (Landers). The discrete, grayish white lesions were seen in the most dependent portion of the vitreous of a patient whose low-grade granulomatous uveitis was a manifestation of his generalized sarcoidosis.

It is possible that pathologic material may be available for the direct study of the vitreous lesions in sarcoidosis at a later date. In that event more tangible evidence will be brought to bear on this problem.

53 Main Street.

Appreciation is expressed for the instruction and help so generously extended by Dr. M. Elliott Randolph, consultant in ophthalmology, Veterans Administration Hospital, Fort Howard, Maryland.

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Fig. 1 (Wholihan). The instrument case and its contents.

A COMPACT INSTRUMENT CASE*

JOHN W. WHOLIHAN, M.D.
Jackson, Michigan

Since ophthalmology requires so many instruments, the resident is at times puzzled as to what basic items he should have at hand to avoid omission of certain fundamental diagnostic steps.

The object of this article is to show that certain simple diagnostic instruments, drugs, treatment medication, and dressings can be readily carried in a small case. This instrument case is the outgrowth of several weeks of working with bulging pockets, frequent lapses in routine which necessitated revisits, and repeated trips to the supply room.

The convenience of the case is only one of its advantages. Besides making the taking of tensions a routine, unless contraindicated, it multiplied the number of interesting cases seen. Several of the large wards at Wayne County General Hospital contain from 60 to 200 patients and frequently other residents, when on rounds, would ask for an

Fig. 2 (Wholihan). The case packed and ready to take on rounds.

* From the Wayne County General Hospital and Infirmary, Eloise, Michigan.

opinion or point out a case with unusual eye findings. The preliminary examination could be instituted on the spot rather than waiting until the resident had accumulated his "tools."

The photographs show the case which measures 9 by 6 by 3½ inches. The leather containers into which most of the smaller and less frequently used instruments fit are Schick razor cases. The contents of the case consist of:

1. Nine 0.5-oz., screw-top bottles containing frequently used diagnostic and therapeutic solutions.
2. Ophthalmoscope.
3. Tonometer.
4. Several visual acuity charts cut from a large chart and a near-vision, reduced Snellen chart.
5. A piece of exposed X-ray film, 5 by 15 cm. for screening.
6. Supply of sterile droppers.
7. Geneva lens measure, exophthalmometer, one-meter steel tape.
8. Several small instruments, epilation forceps, punctum dilator, syringe, and lacrimal canaliculus needle.
9. Condensing lens.
10. Roll of one-inch adhesive tape.
11. Supply of eye pads.
12. Supply of ointments.
13. Scissors.
14. Flashlight and extra batteries.

602 West Michigan Avenue.

EYE-DROP TRAYS

MAX KIMBRIG, M.D.
Huntington, New York

Errors caused by picking up the wrong eye-drop bottle, although rare, have occurred. One automatically checks himself several times before using any eye drops. This, and the fact that the bottle wanted is usually the last one picked up, means decreased office efficiency and annoyance.

The illustration shows an eye-drop tray which I designed and found to be an accurate and efficient aid in eye-drop selection. I made two identical trays for two treatment rooms. I am passing the idea along to anyone who is annoyed with time lost in searching for the right bottle; to anyone who wants to cut down the chances for error.

SPECIFICATIONS

Through a block of wood about 1 by 1½ by 11 inches, bore 10 holes, each ⅝ inch in diameter and about ⅜ inch apart. Glue a piece of cardboard on the bottom and set a ⅛ oz. dropper vial in each place.

A cellophane covered label in front of each hole matches the label on the vial, affording a double check on the vial's contents. This is really a triple check, for one can now reach for a bottle and know its contents by its location. The small vials can be filled from a stock bottle; or those seldom used, such as atropine, can be added to the vial in small quantities.

20 High Street.

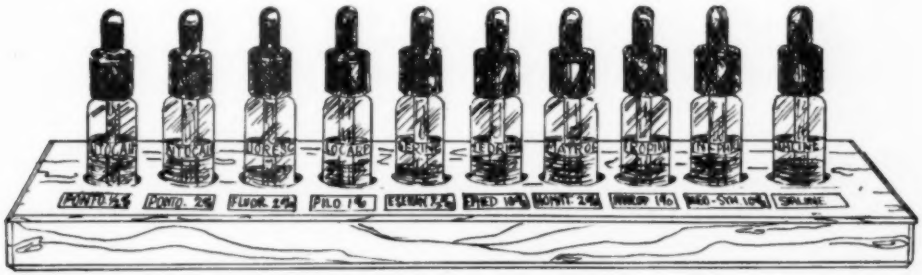

Fig. 1 (Kimbrig). An efficient eye-drop tray. (Drawing by S. M. Lee.)

SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

December 15, 1948

DR. JOHN E. RICE, *presiding*

EFFECT OF PROCAINE UPON THE SPHINCTER MECHANISM

DR. HAROLD G. SCHEIE of Philadelphia discussed this topic. His remarks are here summarized.

Retrobulbar injection of procaine hydrochloride was found temporarily to produce the effect of a ciliary ganglionectomy. The pupil on the injected side, in animals and humans, dilated widely and became fixed. The effect persisted in dogs for 80 to 90 minutes and in humans for 1 to 5 hours. During that period of time, physostigmine was ineffective in producing miosis, but pilocarpine remained effective.

Pupils constricted by physostigmine prior to retrobulbar injection of procaine dilated promptly following retrobulbar injection but pupils constricted similarly by pilocarpine remained miotic.

Pilocarpine, therefore, should be the postoperative miotic agent of choice when prompt miosis is desirable following operations done with retrobulbar anesthesia such as a cataract extraction through a round pupil. Pilocarpine should likewise be used preoperatively when miosis is desirable throughout an operative procedure when done with retrobulbar anesthesia. A peripheral iridectomy, for example, is easier to do when operating for narrow-angle glaucoma if the pupil remains miotic.

Caution should also be taken to instill pilocarpine or a substance with a similar pharmacologic action into an eye prior to the use of retrobulbar injection of procaine hydrochloride for the treatment of acute congestive glaucoma. Failure to do so, or the use of drugs with an eserinelike action alone, would permit mydriasis and very probable aggravation of the glaucomatous state by further obstruction of the angle of the anterior chamber.

Studies were also done to determine the effect of procaine when applied locally to the iris. Prompt pupillary dilatation was obtained in dogs and cats from the injection of 0.1 cc. procaine into the anterior chamber. Pupillary dilatation of some degree was also obtained in human subjects following the instillations of two drops of 10-percent procaine in 1:3,000 phemerol at five-minute intervals. This mydriasis lasted for two hours. A mild cycloplegic effect was also observed.

Pupils dilated by the injection of procaine into the anterior chamber were resistant to all types of miotic agents even those which stimulate the muscle cell directly, such as calcium ions. It was therefore concluded that procaine probably exerts a direct depressant action upon the cells of the sphincter muscle when applied locally. Procaine should probably, therefore, not be used beneath the subconjunctival flap where prompt postoperative miosis is desirable or when miosis is desirable throughout an operative procedure.

Discussion. Dr. David Cogan asked what effect procaine has on the sympathetic ganglion, as far as the pupils are concerned.

Dr. Scheie replied that he had seen Horner's syndrome preceded by injection of the sympathetic ganglion, and that procaine would block a sympathetic ganglion much as it would any other nerve or ganglion.

Dr. Paul Chandler: This paper just reflects the ignorance of the rest of us in regard to this subject—the fact that we are unable to discuss it—and it points up what an original and interesting piece of work it is.

S. Forrest Martin,
Reporter.

COLLEGE OF PHYSICIANS OF PHILADELPHIA

Section on Ophthalmology

December 16, 1948

Dr. Perce DeLong, *chairman*

Plasma cell myeloma of orbit

Dr. Joseph McEvoy (by invitation) said that tumors consisting of plasma cells occur quite frequently in the bone marrow and constitute one of the histologic types of multiple myeloma. Extramedullary plasma cell tumors, on the other hand, are of greater rarity.

A total of 128 cases of extramedullary plasma-cell tumors have been described in the literature. Most of these have been in the mucous membranes. The commonest site of occurrence is in the mucous membrane of the air passages and the next commonest site is in the conjunctiva, where 47 cases have been recorded. The only case involving the orbit that I have been able to find, other than the one described tonight, is the one described by Walsh, which he reports in his textbook on neuro-ophthalmology.

Histologically, the abundance of plasma cells is the outstanding feature of these tumors. The tumor cells are characterized by a large amount of cytoplasm and an eccentrically situated nucleus. The chromatin is arranged in cartwheel fashion, and a paranuclear unstained area is present. Cells with 2 or 3 or more nuclei are common. Other cells such as polymorphonuclears, lymphocytes, and histiocytes, if present at all, are never an essential part of the tumor.

When an isolated plasma-cell tumor is found, the question arises as to whether it is a solitary benign lesion, easily removed, or whether it is a part of the very malignant multiple myeloma. It seems that the microscopic appearance does not play an important role in predicting the clinical course of a given lesion. Even the appearance of mitotic figures in the cells does not indicate malignancy. As long as the plasma-cell tumor is localized and confined to soft tissues and there is no other clinical evidence of multiple myeloma, cure can generally be obtained.

The case to be presented concerns an 80-year-old white woman who was admitted to the medical service of the Philadelphia General Hospital on May 26, 1948. She had no complaints, and was admitted simply for custodial care until admission to a nursing home could be arranged.

Physical examination revealed a well developed, but poorly nourished, anemic, old lady. The general physical examination revealed nothing of note other than the anemia which was hypochromic in type and thought to be nutritional. The right eye was blind. She had had a cataract extraction three years previously. The cornea was densely leukomatous. The left eye showed a senile cataract with vision of 6/60. There was a swelling of the right lower lid which felt like a firm mass extending into the orbit. This mass had been present about three months, was painless, and slowly progressing in size. There was no exophthalmos.

On June 16, 1948, surgery was performed under local anesthesia. The lower lid was incised along its entire length below the tarsus. Nothing was found in the lid itself. Within the septum orbitale was a reddish firm mass with a smooth, apparently encapsulated surface. By blunt dissection it was possible to separate the mass from the surrounding tissues, and follow it back into the orbit beneath the globe. It was shelled out, and removed in toto, measuring 3 by 1 by 1 cm. A large amount of hemorrhage was controlled with difficulty. A pressure dressing was applied. Postoperatively she developed a rather large hematoma of the operative site.

The pathologic report on this tumor is: The material consists of a homogeneous mass of uniformly dark, round cells—plasma cells. There is almost no stroma and practically no mitotic figures are seen. The diagnosis is plasma-cell myeloma.

X-ray examination of the skull, the orbit, the vertebras, the ribs, and the pelvis showed no evidence of bony myelomatous involvement. Repeated urinalyses showed no Bence-Jones protein. The serum calcium was 10 mg./100 cc. Examination of the sternal bone marrow showed no increase in cellularity and hematopoiesis was essentially normal. There was spotty infiltration throughout, with well-differentiated plasma cells.

The serum protein was 10.7 gm./100 cc. Of this 2.4 gm. were albumin and 8.3 gm., globulin.

This extreme hyperglobulinemia was thought to be highly suggestive of a diffuse myelomatous process in spite of the other negative findings.

The patient's right orbit was treated with two courses of irradiation of three doses each. The doses of X-ray therapy were 300 r., 600 r., and 900 r. at three-day intervals.

The postoperative hematoma completely absorbed in two weeks. No remaining tumor mass was discernible, and she was discharged from the hospital to a nursing home on August 24, 1948.

This case was presented as an example of an unusual orbital tumor and the difficulties of evaluation and prognosis of isolated plasma-cell tumors.

Discussion. Dr. Thomas Cowan: I have nothing to add as to the pathologic characteristics of this tumor, but the case does illustrate very well the difficulty of making a diagnosis before excision, and the desirability of excising so as to make a diagnosis. Clinically, the tumor impressed me as being benign by its appearance in the lid, and it had been so diagnosed elsewhere. As the orbit was entered, the characteristics of the tumor became more and more like those of a sarcoma. At its inner attachments it was so infiltrated among the tissues that it was very hard to remove surgically. Following the operation, the healing was very excellent for such an infiltrating tumor.

Dr. Perce DeLong: Plasmocytomas are not rare. However, few have been reported in the orbit.

The plasma cells are not easily recognized, because pathologically they present immature forms of the typical plasma cell, and for this reason are often referred to as myeloma cells.

The metabolic aspect of myelomatosis is interesting, in that it produces a protein in the urine which must be differentiated from albumin by the Bence-Jones test. If found, the diagnosis is quite conclusive. However, its presence is intermittent.

Dr. Joseph McEvoy: You mean the Bence-Jones protein test? Yes, we did it several times, and there was none found, but she did have an extremely high serum globulin.

Endothelial myeloma (Ewing's tumor) of orbit

Capt. Fred Harbert, (MC), U.S.N. (by invitation) and Commander George L. Tabor, Jr., (MC), U.S.N. (by invitation) reported two cases of Ewing's tumor involving the orbit. The term Ewing's tumor is used to describe the clinical entity of a highly radiosensitive primary tumor of the bone which shows no true osteogenesis.

One of the cases presented was primary in the orbit with a rapidly fatal termination in spite of dramatic immediate improvement under radiation therapy. The other case was secondary in the orbit with complete replacement of osteolytic defects by normal cancellous bone following X-ray therapy.

The prognosis in a case of Ewing's tumor is considered to be inversely proportional to the degree of elaboration of recticulum. The histogenesis of Ewing's tumor and reticulum-cell sarcoma are considered to be identical.

Discussion. Dr. Perce DeLong: Ewing's tumors, by the majority of pathologists, are not considered a pathologic entity. It is a syndrome of a nonosteogenic, round-cell, radio-sensitive tumor, and this syndrome can be caused by many types of tumors.

The analysis of Ewing's tumors by many prominent pathologists showed that in a

majority of instances they were expressions of metastasis.

In the child and in the adolescent group, it was also found that they were not truly Ewing's tumors, but neuroblastomas, which proved to be metastatic, and finally, the ones that were primary proved in almost all instances to be reticulum sarcomas. If you notice, Dr. Harbert's second case was finally diagnosed as reticulum sarcoma. Ewing's tumor is not an entity, but a syndrome.

Dr. Fred Harbert: I must, of course, defer to your greater experience and judgment, but just from the standpoint of the clinician I think that Ewing's tumor is still a tenable diagnosis. What are you going to call the characteristic bony lesions when you cannot find a primary tumor, and throughout the subsequent course of the disease, you cannot ever find a primary soft tissue tumor? Ewing himself makes the absence of primary tumor a necessary criterion for diagnosis, so that at least it is a working diagnosis, and may have to remain even after postmortem. The differentiation between Ewing's tumor and reticulum-cell sarcoma is considered largely academic.

Diffuse infiltration of iris associated with nevo-xantho-endothelioma

Dr. Grace R. Nachod presented this paper which includes a brief discussion of the clinical and histologic picture of nevo-xantho-endothelioma together with a case report.

The case is that of a Negro male infant who was first seen because of a sore eye which proved to be due to a diffuse cellular infiltration of the iris and ciliary body with dislocation of the lens and secondary glaucoma. Shortly after the eye was enucleated, he developed multiple skin lesions, one of which was biopsied and diagnosed as nevo-xantho-endothelioma.

Although the cells that had infiltrated into the iris and ciliary body were somewhat similar to those seen in the skin lesion, no definite conclusions could be drawn as to their actual relationship.

Discussion. Dr. John Porter Scott: I speculate as to what would have happened had this eye not been removed. These lesions in the skin have the tendency to regress and disappear leaving no more scars than does chicken pox.

When I saw this child at the time the skin lesions first appeared, I thought that the eye had not been removed soon enough, because, in my ignorance, I assumed them to be metastatic lesions. At that time we had not received Dr. Fry's very excellent description of the tumor. Therefore, we were not sure just what the surgeon's diagnosis was.

Lesions of this type occur in some forms of storage disease. One of these is uncontrolled diabetes, in which xanthomatous lesions may appear. These are more yellow and less pink or salmon in color than the lesions in this child. As in this condition, they may disappear.

In Hand-Schiller-Christian's disease the lesions are yellowish, are larger, and have no tendency to disappear.

This case represents untrodden ground. I could not find any case in the literature in which the tumor was within the eye. One case was reported in which a tumor was in the orbit. I think the ophthalmologists should remember the appearance of this tumor. It would be extreme optimism to think that this tumor would have regressed as did the skin lesions. To repeat, I speculate as to what would have happened had the eye not been removed.

Dr. W. E. Fry: I think there are several features in regard to the eye specimen that might bear emphasis. The first is the infiltration of the iris which was very diffuse and very dense, and in which there were giant cells of the Touton giant-cell type similar in appearance to the Touton giant cells that appeared in the skin lesion, and which I understand are important for the diagnosis of the skin lesion. The eye had been

fixed and dehydrated in ether and alcohol so it was not possible to carry out fat stains. These would have been useful. Fat stains on the skin specimen showed a marked degree of fat.

The other feature that was important was the anterior dialysis of the retina through which apparently the dislocated lens had slipped. Just how this had occurred is entirely speculative. One possibility is that the lens dislocation could have been produced artificially when the eye was cut previous to embedding. This is unlikely, because, of hundreds of eyes that we do cut, if they are cut with reasonable care, no dislocation of the lens occurs, and if it does occur it is not dislocated behind the retina. The secondary glaucoma, probably caused by the dislocated lens behind the anterior dialysis, could have led to severe changes in the eye so that enucleation was indicated.

The question comes up as to whether these lesions in the iris regress. Probably they do, and this is probably why we have not seen them or they have not been reported to any extent before. In all probability, if the glaucoma changes had not occurred the eye might have cleared up, and the lesions regressed spontaneously.

Dr. Herman Beerman: I know the history of this patient and the pathologic findings very well, because I had the opportunity to study the cutaneous specimen, and Dr. Fry was good enough to allow me to study the eye slide. Although Dr. Blank, Dr. Eglick, and I have reported this case from the pediatric-cutaneous standpoints, I hope we have not interfered with Dr. Nachod's plans for publication of the ocular findings.

This is an extraordinarily rare case, and, as was previously mentioned, there is only one other instance in the literature in which eye complications have been noted. This was a patient reported in the discussion of Dr. Lamb and Dr. Lain's paper by Dr. Ellis of Baltimore. No further details are available on this case. Therefore, the present case is unique. I believe it is the first authentic instance in which both cutaneous and ocular complications have occurred, and in which their identity was proved by pathologic examination.

I believe, in retrospect, that when one visualizes the amount of ocular damage present one cannot say the eye lesion would have regressed without necessitating enucleation. I do not believe, therefore, that anyone who handled this patient need fear criticism for the procedure employed.

Dr. A. G. Fewell: I thought the eye should come out, as the whole iris seemed to be thickened and infiltrated with the growth. The tension was rather high, and the eye was apparently blind.

Dr. Grace R. Nachod (closing): I am grateful to Dr. Fry and Dr. Fewell and Dr. Beerman for mentioning the fact that they thought the enucleation was indicated. I wondered about it a little bit myself; and am grateful to Dr. Scott for his discussion.

General Anesthesia in Ophthalmology

Dr. H. H. Stone (by invitation) read a paper on this subject.

Discussion. Dr. Edmund B. Spaeth: Some time ago, while discussing anesthesia for ophthalmic surgery with an anesthetist, not Dr. Stone, this statement was made by that anesthetist, "I do not understand the tremendous differences of opinion relative to general anesthesia which one observes when talking with different ophthalmic surgeons; I doubt whether there is anything more chaotic in surgery than that."

This observation has been made by other men. The fault, or perhaps the reason, for that state of affairs is not strange. There are three factors responsible. The ophthalmologist is only concerned with one of them, namely, his willingness to consider each case for surgery as an individual problem, and in each case whether the surgery indicated can best be done on the patient under consideration with local or general anesthesia.

The second factor is the brief, but rather essential, physical examination by an at-

tending internist, and the consideration of his recommendations as to which kind of anesthesia is to be used.

The third factor is the anesthetist's problem. Which type of anesthesia is to be used, inhalation anesthesia, intravenous anesthesia, or rectal anesthesia? All have optimum indications for use; each handles best a group of situations present. It is seldom, in recent years, that we suggest the type of general anesthesia to be used. Our wishes should be considered as to whether the surgery should be done under local or general anesthesia; but the anesthetist and the internist are responsible for the type of anesthesia to be used on each patient.

There is no doubt whatsoever but that the increase in the use of general anesthesia is directly proportional to the efficiency and the understanding of ophthalmic surgical problems by the anesthetist. We feel unusually fortunate to have Dr. Stone for our surgical cases.

Because of his efficiency and his department, we now view anesthesia quite differently. In the past, general anesthesia was used only when absolutely necessary. At the present time it has become the choice in many surgical procedures. Intraocular operations are still to be done under local anesthesia if possible; on the other hand, one need no longer dread them under general anesthesia, nor need one fear postanesthetic accidents and complications. This is quite a reversal in practice.

Plastic surgery, even the relatively minor procedures, can be done so much better without infiltration and/or block anesthesia otherwise necessary. Lacrimal-sac surgery, with its rather exacting anatomic dissections, is definitely simpler when performed under general anesthesia.

All types of muscle surgery, regardless of the age of the patient, are shortened in operating time and simplified without injections into the capsule sheaths which are necessary to make that surgery painless. Surgery for retinal separation, which can vary from a relatively brief period of operating time to hours on the operating table, when done under general anesthesia is far less taxing to the patient, and very much easier for the surgeon.

These procedures need little if any change in essential techniques regardless of the type of anesthetic which is used. Intraocular surgery, when done under general anesthesia, must have certain rather important changes in the surgical technique, connected with fixation of the globe and the support of the lids. This is outstanding with corneal grafts; in fact, it is so important with this latter type of surgery that it is used also at the first dressing of the patient's eye.

In the final analysis, a paper such as Dr. Stone has just given us has greater significance to anesthesiology than to ophthalmology. The anesthetist cannot take care of ophthalmic cases unless we are willing to permit it, and to coöperate with him at the same time. General anesthesia should play a bigger role in ophthalmic surgery than it does, considering, naturally, the availability of trained medical specialists in anesthesiology.

Dr. H. H. Stone (closing): Up to the present time we have had no fatalities. We occasionally do get into difficulty, and I think you get into difficulty no matter what type of anesthesia you use. We have seen difficulty with local anesthesia. Not especially in eye surgery, but we have had two fatalities when general surgeons were using local anesthesia. The expert should give the anesthetic for ophthalmic surgery.

I feel there is not a more difficult case than the cataract extraction under general anesthesia, not barring chest surgery. It takes far greater skill to keep these patients breathing yet not coughing or sneezing when the cataract is removed, and keep them well oxygenated throughout the entire procedure, than is required for a 5 or 6 hour pneumonectomy.

M. Luther Kauffman,
Clerk.

CHICAGO OPHTHALMOLOGICAL SOCIETY

December 20, 1948

Dr. A. C. Krause, *president*

Clinical meeting

Presented by the Department of Ophthalmology, Northwestern University Medical School.

Convergence insufficiency

Dr. Bruce McClellan presented a 37-year-old man who was first seen at the eye clinic about one month ago, with a complaint of headache associated with eyestrain and a "drawing sensation" about the right eye. His eyes have turned out since he was a child, but medical advice had not been sought until the symptoms became worse.

Examination showed 20/20 vision in each eye; refraction showed a +0.75D. sph. with a small cylinder for each eye. On the screen test for distance he measured 45 prism diopters divergence for distance and 65 for near, with a left heterotropia of 4 diopters for distance and 2 for near; these measurements have been repeated on three successive tests. His near point is remote; however, this is not a true case of heterotropia because he can fuse; he can fuse for near, the near point being forced to 110 mm. on the first examination, and, on the second, to 90 mm. with the right eye deviated. He prefers the left eye for distance and for near. There is marked underaction of both superior recti muscles, the right more so than the left; also underaction of the medial rectus muscles.

The diagnosis in this case was convergence insufficiency, secondary to divergence excess, also bilateral superior rectus paresis with overaction of both inferior oblique muscles.

Discussion. Dr. Beulah Cushman felt that the convergence insufficiency is secondary to the divirgence excess, which always becomes a complication sooner or later. It becomes apparent as the accommodative power is reduced. This patient at the age of 37 years is having difficulty maintaining single vision for near work; the divergence for distance has been present since youth. The vertical anomaly is the primary factor. Surgery will include first the correction of the convergence insufficiency with resection of the medials and recession of the overactive oblique; at the second step there will be recession of the laterals.

Dr. E. H. Merz said the surgery mentioned will correct the vertical anomaly and the horizontal can be corrected at a later date. As Weidman states, most horizontal errors are secondary to vertical abnormality. It has been reported that these conditions can be corrected with tenotomies of the inferior oblique or recessions.

Dr. Kirby and Dr. White have commented on conditions where complete tenotomy has resulted in complete paralysis of the inferior oblique. If there is complete paralysis of the inferior oblique and of the superior rectus, there is a posterior head tilt which is undesirable.

Dr. Scobee has reported a case of bilateral paralysis following surgery in which pseudoptosis resulted because of the marked back tilt of the head. The congenital paresis is due to an error in cleavage of the common premuscle mass. These conditions are not uncommon. White, Kirby, and Dunnington say they are the most common of all muscle conditions. The superior rectus muscle differentiates from the group later than any other, and for that reason more congenital anomalies are found in that muscle.

Fracture of frontal bone

Dr. Paul R. Irvine reported a 10-year-old girl with a history of a fall from a bicycle. Whether she suffered a concussion is not clear; she was said to have struck the right side of the head on the handlebar or a rock. At the time, nothing was noted except slight discoloration at the right outer canthus. Approximately one hour after the accident some

swelling was noted about the eye. This became more marked and, 48 hours later, she was seen by an oculist. On the suggestion that a hematoma was present a conjunctival incision was made but no blood drainage resulted. About five days later nausea and dizziness occurred and she was put to bed, without improvement.

Ten days ago she was first seen at Passavant Memorial Hospital. On examination the right eye was proptosed and depressed. Vision was: R.E., 20/200; L.E., 20/20. Palpation over the lacrimal gland revealed a mass which was thought to be a dislocated lacrimal gland; a smaller mass was noted nasalward. X-ray films showed fracture of the frontal bone extending into the roof of the orbit. Neurologic consultation advised conservative management; they felt there was not only a hematoma but a cerebrospinal leak. On dismissal she had no diplopia.

Discussion. Dr. Derrick Vail said that this case emphasizes that one should not be too hasty in entering an orbit for acute proptosis even with the practical certainty that it is due to subperiosteal hematoma from injury. It is not unusual to find reports in the literature of acute proptosis due to hemorrhagic extravasation under the periosteum in patients who had scurvy, particularly infants.

When the X-ray films in this case were received from the family doctor, surgery was scheduled. As a precaution, however, further X-ray studies were made which showed the fracture and the operation was therefore cancelled. The fracture, as shown on the slides, extended into the roof of the orbit. The family doctor had mentioned that, on inserting a needle, he had withdrawn about 0.5 cc. of clear fluid; that report should have led to the suspicion of a leak through the roof of the orbit of cerebrospinal fluid. It is, however, not unusual to obtain some fluid from the orbit on diagnostic puncture in cases of acute proptosis; fluid from edema, for example, can be drawn into the syringe.

Certainly, in this case, conservative treatment was well worthwhile. The neurosurgeon feels that the crack will heal fairly well and if, at the end of six weeks or so, there still remains definite proptosis, particularly if a swelling is palpated in the roof of the orbit, a small incision to see if there is an encapsulated hematoma is probably justified.

Progressive meningioma

Dr. R. D. Tebbett presented two cases. The first was that of a 54-year-old white woman who complained of gradually increasing weight for 17 years, blindness of the left eye for 10 years, and failing vision in the right eye for one year. In 1931, she weighed 131 pounds and at present she weighs 245. In 1940, she got something in the right eye and as she rubbed it she noted that the left eye was completely blind. Apparently the cause for the loss of vision was primary optic atrophy, but the cause was not determined. She was told that the right eye would probably never be affected. In January, 1948, she noted decreasing vision in the right eye, with what she described as a gray area in the lateral part of the field. Glasses were prescribed which improved the vision somewhat.

When she entered the hospital in July, 1948, vision in the right eye was 20/70. The left eye showed a cataract and primary optic atrophy. The right disc was pale; the scotoma descended from above laterally to the fixation point. Neurologic examination was essentially negative; spinal fluid was normal. X-ray studies of the skull showed proliferative changes of the inner table of the frontal bone and the rostral and dorsal portion of the sphenoid. It was decided that she had a meningioma which had probably been progressive for 10 years or more. Surgery was not advised.

Tumor of orbit

The second patient, presented by Dr. Tebbett, was a 33-year-old white woman who had had proptosis of the left eye, apparently of mild degree, for 3 or 4 years. Ten days prior

to entry she noted increase in the proptosis; in fact, the eye herniated between the lids. She entered the hospital for observation, and a lateral tarsorrhaphy was done to prevent further herniation of the eye. Previous X-ray studies were reported as negative.

Eye examination was essentially negative with the exception of the proptosis which measured: R.E., 13 mm., L.E., 27 mm. The eye was proptosed directly forward without lateral displacement. Visual fields were normal. Neurologic consultation was essentially negative. There was no bruit over the proptosed eye. There was a question of frontal-lobe disturbance because of the slightly disturbed judgment of the patient during questioning. X-ray films at this time showed marked erosion of the optic foramen on the left side, erosion of the lesser wing of the sphenoid, and erosion of the greater wing of the sphenoid.

Operation was performed by the neurosurgical service and a dumbell-shaped tumor was found, the greater part of the mass lying in the middle fossa extending up through the left optic foramen and into the orbit. The entire multiloculated tumor was removed at the time of operation. The pathologic report is, as yet, debatable. It has been reported as a neuroma and also as a meningioma.

Discussion. Dr. Derrick Vail felt that these two patients were most instructive for demonstration because they emphasize so clearly the point that one cannot ignore optic atrophy or dismiss it lightly without being satisfied that every possible avenue of investigation has been exhausted—even then it should be considered as an unsolved crime, which should cause concern to the ophthalmologist. If the first patient had had the proper diagnosis, early surgery could probably have been done. After 10 years of obesity, increased blood pressure, cardiac and arteriosclerotic changes she was not a suitable neurologic risk.

This woman's youngest child is about 8 years old and she feels, as does the surgeon, that it probably would be best, with a slowly-developing malignant tumor—not malignant in the sense of metastasis but in destroying the adjacent tissues—to go on, with the possibility of keeping a small degree of sight, gradually getting worse, but at least keeping her life during the next few critical years of bringing up this child. She knows the whole story, has the utmost courage, and has faced the issue most cheerfully. Had surgery been attempted the neurosurgeon felt that a fatal result was pretty certain.

The second case is an example of the same situation. The patient had proptosis for 10 years, gradually getting worse, and more or less ignored the condition. Five years ago she consulted an ophthalmologist who found some proptosis, but the X-ray report was negative and he felt that there was no particular reason to account for the proptosis. An interesting feature of this case is that the proptosis is directly forward, which would indicate disturbance in the muscle cone; also that the vision is entirely normal in each eye and, third, that the optic nerveheads were entirely normal; the fields of vision were entirely normal; and there was no interference with ocular movements and no diplopia.

The situation became critical when she had sudden herniation of the eye, a catching of the upper lid behind the proptosed eye, which alarmed her considerably and she sought help. The X-ray film shows a striking phenomenon; complete erosion of the entire outer wall of the optic foramen. To take a picture of the optic foramen requires special technique and the X-ray man must be instructed to get a good view of the optic foramen. Extensive erosion of the sphenoid wings is also shown. Not many conditions produce such a picture—proptosis with erosion of the optic foramen and sphenoid wings.

The first thing to be considered is meningioma, and meningiomas are not unusual in females particularly. The second thing is

aneurysm, but there was no suggestive history and aneurysm would have undoubtedly interfered with some of the ocular movements. In view of the experience of Dandy, Cushing, and Eisenhardt—whose monograph is one of the classics of ophthalmic literature—it was felt that to perform an orbital operation in this case would be a mistake, and that the transfrontal approach was necessary.

Almost all cases are not purely local in the orbit, but secondary, by extension through the apex of the orbit from a meningioma arising usually on the lesser wing of the sphenoid. To give the patient every chance possible, the transfrontal approach must be used because, if there is proptosis plus bone changes, it is evident that an intracranial tumor extending into the orbit is present. To do an orbital exenteration only is but half the job; whereas, by transfrontal approach the neurosurgeon skilled in his work can unroof the roof of the orbit and find the tumor, as was done beautifully in this case.

It is a mistake, therefore, for the ophthalmologist to carry out orbital exploration, particularly in view of the possibility of meningioma. It is gratifying to report that this woman is recovering well, the proptosis has entirely receded and it is now just a matter of complete convalescence to be followed later by opening the lids.

These two cases should, therefore, emphasize that one should not be content with a purely objective diagnosis of optic atrophy, but should seek the cause, and should not be satisfied until that cause is found.

Dr. James E. Lebensohn: The first case, in which there was optic atrophy in one eye and central scotoma with expansion temporally, is probably one phase of the Foster-Kennedy syndrome; in fact, the Foster-Kennedy syndrome is more often found with suprasellar meningiomas than with frontal-lobe tumors.

The development of field changes is interesting. Pressure produces primarily a central scotoma which expands centrifugally, hence producing first a temporal pallor and then the picture of primary optic atrophy. On the other hand, the papilledema on the central-lateral side shows primary loss in the peripheral field, continues with centripetal contraction until finally secondary optic atrophy results. Among the significant findings that distinguish secondary optic atrophy of this type are occasionally concentric rings around the optic disc.

Pituitary adenoma is only one of the possible causes of bitemporal hemianopia. Similar effects on the chiasm may be produced by meningiomas, glioma of the chiasm, aneurysm of the anterior cerebral artery or its communicating branches, and chiasmal arachnoiditis. Careful study should indicate the differential diagnosis in any particular case.

Scientific Program

Primary lipid dystrophy of the cornea

Dr. Daniel Snydacker presented the case of a Negress, aged 20 years, with an unusual bilateral, symmetrical, ring-shaped corneal opacity. The appearance of the lesion, the lack of a demonstrable etiology, and the presence of an elevated blood cholesterol pointed to the diagnosis of a primary lipid dystrophy of the cornea.

Discussion. Dr. J. V. Cassady mentioned a similar case which he had had under observation. The patient was a 56-year-old woman who had a central type of xanthomatosis of the cornea rather than the peripheral type presented by Dr. Snydacker. There was a deep, central, yellow, vascularized corneal opacity in one eye, which had gradually developed without antecedent trauma or inflammation. Occasionally it was irritated and red, but usually without subjective symptoms other than blurred vision. Katz and Delaney described a similar central lesion in lipid dystrophy of the cornea. Dr. Robert von der Heydt confirmed the diagnosis in this case. The Wassermann and Mantoux tests were negative; the patient had 225 mg. blood

cholesterol, hypercholesterinemia. Vision in the other eye was normal, although many cases are bilateral.

Dr. Peter C. Kronfeld had observed for some time a patient whose eyes are similar to those of Dr. Snydacker's patient. Little was known of the history in this case. Her two sisters were blind from a gross form of this dystrophy and, while he had not seen them, they had been described by an eye doctor in their home town, and the corneas were completely opaque. In the two sisters, the disease took the same course as in the woman under observation. All have marked hypothyroidism and all are much overweight, none weighing less than 220 pounds. The symptoms started during the third decade of life. The patient under observation still has 20/20 vision in each eye. She has been put on a diet of 1,000 calories a day, plus vitamins. Her blood cholesterol is high, and the determination on one of the sisters was also high.

Dr. Robert W. Zeller said that, after a previous admission at Cook County Hospital in 1946, this patient again came under observation in 1948. In 1946 there was a flareup of the keratitis following injection of tuberculin; it was felt that the keratitis might have been on an acid-fast basis. She was not seen for two years when she returned because of a fractured vertebra.

The basal metabolic rate was then −23; subsequent determination were −17 and −9. The first determination was probably the most significant of the three. Total cholesterol was 186 mg., within normal limits. Total protein determination was 7.6, albumin was 4.2, and globulin, 3.4, which is rather high. The cephalin flocculation was 1+ positive. Thymol determination was 7.4 units; the upper limits of normal at County Hospital Laboratory is 5 units.

The biochemist felt that these determinations indicated possible minimal liver damage; he also said that the thymol determination had to do with determination of lipids in the blood and, if elevated, might substantiate the diagnosis of lipid dystrophy.

This case was seen by Professor Van Ness who was here from Finland. He has apparently had a case of true lipid dystrophy, one of the seven reported. He felt that this was a case of lipid dystrophy also. It might be worth while to use choline in this patient, following Dimitry's suggestion. It is known to be a fat solvent, and might possibly bring about dissolution of the opacities.

Dr. Daniel Snydacker (closing): In answer to Dr. Zeller's question about the use of choline, it is doubtful if this would be of value because the opacities are deep and the choline probably could not reach them, and the basis of the treatment involves actual contact.

Choice of operation in acute glaucoma secondary to swelling of the lens

Dr. Paul Sternberg and Dr. Samuel J. Meyer presented a paper on this subject and discussed choice of operation for an eye in which glaucoma is secondary to lenticular intumescence. It is believed that the acute, congestive glaucomatous attack which is said to be secondary to lens swelling occurs in an eye that may be termed preglaucomatous. The opposite eye is frequently of the preglaucomatous description, with a narrow entrance to the angle of the anterior chamber.

An iridectomy, if done early, or, if done later, an iridencleisis are the operative choices for reducing the increased intraocular pressure. An intracapsular cataract extraction is performed subsequently with use of corneoscleral sutures.

Discussion. Dr. Derrick Vail agreed with Dr. Sternberg that, in one's experience, glaucoma due to an intumescent cataractous lens will be encountered sooner or later. The essayists have given clear indications for various types of surgery in this condition, but he differed on some of the points expressed.

The glaucoma is due entirely to the swol-

len lens; that is a mechanical fact. Whether or not the angle is narrow prior to development of the intumescent lens is not pertinent to this discussion, because in any cataract case, if the lens is allowed to remain and become intumescent, there will be a rise in intraocular pressure at some time or other.

This occurs when the swelling of the lens reaches its maximum and may not precipitate an acute attack, but will result in a period of increased intraocular pressure followed in time by decrease in pressure as the intumescence recedes.

A mature cataract undergoes a varying process of evolution, eventually leading to the morgagnian type where the nucleus falls to the floor. If the morgagnian cataract is permitted to remain, the milky lens material eventually absorbs if it does not leak out through a spontaneous rupture of the anterior or posterior capsule, in which case there is bound to be considerable difficulty in the eye with iridocyclitis and secondary glaucoma. If the capsule remains intact the milky substance generally absorbs, leaving the condition that has been described in the literature: a shrivelled nucleus held between two collapsed capsules; in which case, of course, the glaucoma is not a problem because, if it did exist, it had spontaneously taken care of itself.

The point about the narrow angle as a provocative condition deserves considerable emphasis. It certainly should make one more careful in the study of these cases, particularly so far as the opposite eye is concerned. In ordinary acute glaucoma due to an intumescent lens, the lens should be removed as the primary cause of the glaucoma. In the literature there are described the use of pilocarpine and preliminary operations such as iridectomy and iridencleisis, which are apparently not necessary; in an experience with 10 or more such cases, the cataract has been removed successfully even in the presence of high intraocular pressure and a congested eye. The lens may be removed in its capsule by the Smith method and, on the second or third day following, the eye is white and obviously grateful for the surgical interference. As Colonel Smith has said, the lens in such cases may be dislocated almost by "an angry look." To try to deliver the lens with capsule forceps is almost futile, because it is like trying to pick up a piece of soap in the bathtub.

A procedure recently advised by Dr. Daily is to prick the capsule with a small needle, letting out some of the material which, in turn, reduces the intumescence and permits grasping the capsule with forceps. Another method described is to open the capsule with a diathermy coagulation needle as a preliminary step. That seems rather involved when a needle will serve the purpose. Some men have had success with the erisophake, but in his own hands the Smith operation for this type of case is ideal.

An illustrative case is one of a patient operated on, in 1915, by Dr. Derrick T. Vail, Sr., at which time a cataract was removed from the right eye. The patient was satisfied with the result, he saw well, and was advised to have the lens removed from the other eye, which advice he ignored and went on for 10 years, the lens, of course, becoming more and more mature.

When seen at that time the lens was becoming hypermature and removal of the cataract was again advised. Six or eight months later he came in with an acute attack of glaucoma. He was almost 80 years old, had a vascular hypertension of 200+, he had had a coronary attack about two years before, he had nephritis, and could not possibly have been a worse risk.

However, although the problem was approached with fear and trembling, the incision was made ab externa, as so ably described by Dr. Meyer, the incision was enlarged with scissors, sutures were placed, and an iridectomy was done.

In doing the iridectomy the lens came forward and it was just a matter of touching

it gently through the cornea to deliver it by the Smith method. Surprisingly, an expulsive hemorrhage did not occur and the eye turned out very well indeed; the second day following operation it was as white as in the ordinary case and the patient made a complete recovery without any complications whatsoever. Thus, in certain conditions, one is justified in performing an intracapsular operation even in the presence of a high degree of glaucoma.

Possibly one reason why iridectomy has failed in these cases is because anterior peripheral synechias have developed, as pointed out by the essayists. It is not certain that an iridencleisis in these cases is advisable, because the angle is already blocked by the intumescent lens, and although the essayists have demonstrated that this is a theoretic objection, it is conceivable that one will temporize and delay and lose valuable time in permitting filtration to function. Such an eye is subjected to two procedures rather than one.

Intraorbital aneurysm

Dr. Robert F. Heimburger (by invitation), Dr. H. Robert Oberhill (by invitation), Dr. H. Isabelle McGarry, and Dr. Paul C. Bucy (by invitation) presented a paper on this subject and reported a case of exophthalmos due to aneurysm of the lacrimal artery contained entirely within the orbit. Transcranial exploration of the orbit and removal of the aneurysm of the lacrimal artery resulted in the patient's recovery.

A survey of the literature shows no other verified case of aneurysm of the lacrimal artery and, consequently, the criteria for differential diagnosis cannot be set up. Unilateral exophthalmos without pulsation but with evidence of venous obstruction, increased intraocular pressure, and failing vision were the clinical manifestations of the case presented.

Discussion. Dr. Paul Bucy was surprised to find that these are such uncommon lesions and that even those cases so listed in the literature are practically all questionable. In view of that fact it is even more remarkable that Dr. Kronfeld made the correct diagnosis preoperatively. This is an interesting problem, one which can be best dealt with if the lesion is in full view, as is possible with a transfrontal operation.

Dr. Peter C. Kronfeld recalled that when this patient was first seen she had progressive exophthalmos, ocular hypertension refractory to everything that was tried, limitation of ocular motion, swelling of the disc, and retinal hemorrhages. By this neurosurgical operation she has been cured. The present function of the eye is normal. One thing that was perhaps omitted was a more thorough study of the ocular hypertension. It apparently was a case of hypertension due to interference with venous outflow; somehow the aneurysm interfered with outflow of one or both ophthalmic veins; it would have been interesting to study this more in detail. It looked alarming and since it was felt that it was probably an aneurysm, the patient was referred to the neurosurgeon. In watching the operation, it is apparent that there is no possibility of exposing such a lesion equally satisfactorily through the anterior aperture of the orbit. While the great advantages of the transfrontal, transcranial approach to the orbit have been appreciated, this particular case is convincing proof that many cases of orbital tumor deserve the transcranial approach.

Richard C. Gamble,
Secretary.

AMERICAN JOURNAL OF OPHTHALMOLOGY

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EPILOGUE

Flying 25,000 feet above the Atlantic ocean; behind, two weeks of American hospitality; in front, the old routine of work; it seems a good moment—the first opportunity in two weeks to sit back and relax—to send American ophthalmology a "thank you."

These two weeks have indeed been full to overflowing—one at the academy meeting at Chicago, a week-end at St. Louis with the local ophthalmological society and the American Board of Ophthalmology, followed by a week with the American College of Surgeons again at Chicago—two weeks of scientific papers and exhibitions, of social and academic functions, a whirl of events guided with what appears to be effortless efficiency, from companionable breakfasts through the crowded sequence of the day to the boundless hospitality of the evening and the good fellowship of the early morning.

This was the first academy meeting I have attended. I have taken part in many meetings in many countries; but there has been none like this. My main impressions were of the vastness of the meeting and the ordered rush of 4,000 members (all so enthusiastic)

and almost 4,000 wives (all so delightful); the immense caravanserai of a hotel that absorbed them into its interstices like a hydrophilic gel, apparently without effort or disturbance of its normal routine; the crowd of events that can be fitted into a day; the excellence and variety of the scientific program; the amount and the modernity of the scientific equipment on exhibition; and finally, and by no means least, the value and comprehensiveness of the courses of instruction—a feature unique to the academy which must be of immense educational value to the more isolated practitioner, whereby each year he can refresh himself in fundamental procedures and acquaint himself with recent advances at the hands of acknowledged authorities. But the most pleasant time of each day was the hour before dinner when everyone "visited" and I met intimately the many friends who have now become an accepted part of my life.

Without doubt the academy is one of the most important influences in American ophthalmology. The atmosphere of the meeting with its nice balance between professional and social activities, between what is new (as seen in the papers presented) and what is established in ophthalmology (as seen in the instruction courses), is an immense stimulus to the visitor and must be an equal stimulus to those practicing in a country wherein distances are measured in thousands of miles; but one hopes that it will not become much bigger and busier lest it topple over by its own weight or explode. So far as the present meeting was concerned, the burden thrown upon its organizers must be immense, but it is a burden that they can obviously carry and it was a pleasure to witness the effortless ease with which Conrad Berens presided over it, aided immensely by the charm of his wife.

The American College of Surgeons formed a second week of equal interest, but with 5,000 delegates instead of 4,000—the same high standard and breadth of scientific proceedings and the same good fellowship. The highlight of this meeting was the colored television—a thousand people at a time could follow in its detail an operation for cataract carried out, with a running commentary by the surgeon, in a hospital in another part of the city. In this meeting, however, ophthalmology occupied a small corner. Is that wise? If ophthalmology stands alone outside the umbrella of general medicine and surgery, it will lose much of its inspiration and philosophy.

In both these meetings the outstanding impression carried away by the European visitor is their vastness. For example, at the convocation of the college almost 1,000 candidates were initiated into the fellowship at one time. This is the greatest difference between America and Europe. In Europe the standards are as high and the men as good; but the mass and weight of America must give it an immensely preponderating influence in world medicine. With this comes responsibility—a responsibility which America must accept, and is indeed accepting with enthusiasm and confidence.

Stewart Duke-Elder.

PIGMENTED TUMORS

The beautiful exhibit of Dr. Arnold Zimmerman at Atlantic City which displayed the results of the work of an anatomist on a dermatologic problem is of the greatest interest to ophthalmologists. His preparations showed clearly that the pigmentation of the skin does not arise by synthesis of melanin in the epithelial cell. Instead it is elaborated in specialized branched cells called melanophores which invade the embryo skin from afar and transfer their melanin to epithelial cells.

It seems not unreasonable to speculate that the cells of the choroid also receive their pigment from specialized pigment-bearing cells if, indeed, the melanophores of this membrane are not actually similar cells that have originated in the embryonic neural crest. If this is true, then the tumor known

clinically as sarcoma of the choroid is actually a neurogenic tumor.

A dozen years ago Georgiana Dvorak-Theobold (Tr. Am. Ophth. Soc., 1937) thoroughly reviewed the subject and suggested that the most tenable hypothesis is that of Masson in whose opinion the cells of these tumors, as well as of nevi, are derivatives of the cells of the sheath of Schwann. There still is doubt about the origin of the cell. Recent studies of the origin of melanoblasts, or cells that elaborate melanin, are most suggestive and may point the way to a solution of the complex problem.

There is of course no conclusive evidence that the origin of the pigment-bearing cells of the choroid have the same origin as the melanophores elsewhere in the body but it is at least probable that this is true. It has long been accepted by zoologists that the pigment-producing cells of amphibia and birds arise from the embryonic neural crest. The melanoblasts of mammals were thought to have a different origin.

The recent experimental work of Mary E. Rawles (Physiol. Zoöl., **20**:248, 1947; Physiol. Rev., **28**:383, 1948), however, supports the view that this is not true. She tested the potency of various portions of mouse embryos of a homozygous black strain ranging in age from 8 to 12 days' gestation by isolation and transplantation into the celom of white-leghorn chick embryos of 60 to 65 hours' incubation. In this site the transplants were allowed to grow until the host hatched. Isolations were made at various axial levels of the embryo in such a way as to test tissues of the central nervous system, adjacent tissues of the somite, and lateral plate and limb-bud regions for pigment-cell production in the grafts.

It was clearly shown that melanophores can be produced only from tissues that contain presumptive neural crest, histologically recognizable neural crest, or cells in migration from the neural crest. Skin and hairs that were completely normal except for the absence of pigment and pigment cells grew in all the grafts whenever neural crest had been excluded.

The development of structurally normal white hairs from a potentially pigmented mouse is conclusive proof that the formation of melanin pigment in the ectoderm and its derivative, the hair, is entirely dependent on one particular type of branched pigment-forming cell, the melanophore, which originates in the neural crest. Several hundred grafts were made.

That epithelial pigment in man also arises in neural melanoblasts was shown by Zimmerman and Cornbleet (J. Invest. Dermat., **11**:383, 1948) who studied the development of epidermal pigmentation in the Negro fetus. Specimens of skin were taken from the scapular and abdominal region of 50 fetuses obtained by abortion.

Dendritic melanoblasts, with incompletely elaborated melanin, appear in the third month and from their first appearance do not resemble epithelial cells. They give a faintly positive dopa reaction which indicates that they elaborate an oxidase that is essential to the synthesis of the melanin, and epithelial cells do not. The melanoblasts progressively pervade the epidermis through the intercellular spaces and form an intricate pattern by their long processes. The epithelial cells acquire melanin secondarily by transfer from the dendritic processes of the melanoblasts.

Carcinomas that arise from the pigmented basal layer of the skin are only moderately malignant; whereas, the melanoblastic neoplasm is wildly malignant. The latter has a tendency to spread in sheets along preformed surfaces. The sheath cells, which are thought to be the cell from which choroidal sarcoma originates, are indeed sister cells of the melanoblasts but they give rise to sarcomas that are sparsely pigmented, if at all.

It is also interesting to note that workers in diverse areas of thought are uncovering interesting related data on the origin of pigment cells and that their findings all sup-

plement and support each other without essential reservation.

That this is true justifies the belief that in time the work now in progress will also clarify the specifically ophthalmic problem of pigmented tumors.

F. H. Haessler.

TRAINING IN OPHTHALMOLOGY

The American Board of Ophthalmology examinations afford an excellent opportunity to evaluate the present-day training available for men wishing to enter ophthalmology. Here it is possible to compare the knowledge acquired by the candidate in the various training facilities.

In certain circles there is the opinion that unless a man has had a regular residency in one of our better-known training centers there is little opportunity for him to acquire sufficient knowledge to become a "safe ophthalmologist." The examinations have shown that this is not the fact.

The individual who has a regular residency has definite advantages. His time is planned and the work in the basic sciences is supervised and often spread out over a sufficiently long time to make it simpler for him to acquire the knowledge. He is assigned to the laboratories where, at his leisure, he may work and study. Time is set aside during which various men in the department devote their energy in teaching him the clinical aspect of the specialty. He is taught to write and present papers. He has the advantage of working in the clinic and hospital in company with other residents. His evenings are free to study or, in some centers, to attend lectures. All in all it is an ideal and pleasant method of obtaining training.

Unfortunately, not all residencies live up to this ideal method. In some clinics the resident is used for the benefit of the organization without the organization giving its fair share in return. From the examination of candidates from such institutions it is apparent that little time has been spent in supervision or teaching. That this supervision is necessary is very apparent. There have been some instances where the chief of the department lost interest in the teaching of residents and the candidates coming up for examination under this regime show lack of proper training.

What of the man who has been denied the privilege of a residency and who must depend upon a preceptorship for his training? The examinations have shown that it is possible to obtain an excellent training by this method. It does, however, require a longer time. In addition, there must be the "will to win" as the man must do his studying at night when he is fatigued from a hard day's work at the office. The examinations have also brought out the fact that in most instances it is necessary for the student to take a course in the basic sciences. Whether it be one of the longer courses or the very concentrated course of the Ophthalmological Study Council (The Lancaster Course) appears to make little difference.

In the preceptorship much depends upon the preceptor. If the candidate is to be properly trained the preceptor must be a sound ophthalmologist who is willing to take the necessary time to teach the clinical aspects of ophthalmology. One of the candidates, who received his training from a short basic-science course and a preceptorship and who was given one of the highest average grades, was asked regarding his training. His preceptor, in one of the small communities in Texas, spent a certain amount of time each evening after office hours discussing the cases of the day that offered unusual problems, thus allowing the student the opportunity to acquire clinical knowledge and judgment.

Thus the examinations have brought out the fact that, while a carefully supervised residency is the ideal method of obtaining a training in ophthalmology, it can be obtained from a combination of a basic-science course and a preceptorship. The examinations have also shown that a man may go through a

poorly supervised training to make him a safe ophthalmologist. It therefore becomes evident that those in charge of the training of younger men in ophthalmology, whether in a residency or a preceptorship, assume a grave responsibility in making certain that these men receive the necessary personal supervision and instruction.

Frederick C. Cordes.

GOETHE AND COLOR

During his life, and even more since, Johann Wolfgang von Goethe has excited homage and adulation. His family home has been quickly rebuilt after the war's destruction. The mineral, goethite (hydroxide of iron), was named in his honor. The bicentennial of his birth, August 28, 1749, received world-wide attention. A universal man of genius, like Leonardo da Vinci and Benjamin Franklin, Goethe was a writer, poet, statesman, theatre director, and naturalist.

Before completing his law course at Strasbourg, in 1770, Goethe had a serious pulmonary hemorrhage and, during his lengthy convalescence, pored over books on occult philosophy, alchemy, astrology, and religious mysticism. Converted finally to the philosophy of Spinoza, he henceforth considered individual creeds and dogmas unnecessary.

While in his student boarding house, he was impressed by the enthusiasm of the students of medicine. . . . "These, as is well known, are the only students who discuss with energy out of school hours their science and profession." He visited the clinics, watched Schilling in his expert cataract surgery, and observed attentively as Lobstein performed a type of dacryocystorhinostomy on his companion, Herder. Goethe felt strongly that "The physician must be creative if he is really going to heal. If he is not creative then he . . . will be a mere bungler at his work."

Goethe's literary productions from 1771 to 1775 gave him renown and influential friends. In 1775, he was appointed state councilor at the Saxon capital of Weimar, and his concern with the productive capacity of the duchy restimulated his interest in the natural sciences. His scientific thinking was speculative, poetic, and intuitive rather than empirical, analytical, and critical. Everywhere Goethe sought for and found continuity. "The plant goes from knot to knot, closing at last with the flower and the seed. So the tapeworm, the caterpillar, goes from knot to knot and closes with the head. Man and the higher animals are built up through the vertebrae, the powers being concentrated in the head." Goethe had the view that all variations in plants and animals were only metamorphoses of a primitive archetype, and not evolved one from the other, as Darwin later enunciated.

Being an amateur artist, Goethe studied pictorial art in 1768 and from this stemmed his interest in anatomy and color. Peering through a prism at the broad luminous surface of a sheet of paper on a dark background, he noted that he saw the colors only where the white paper and the dark background had a common boundary. He immediately concluded that Newton's theory is false, and that every color was merely the mixture of light and darkness in new proportions. The prism only served to move light and darkness over each other. He rejected the "artificial" theory of seven colors —the fundamental colors were just black and white. Color was solely a problem of sensory perception and he abhored the intrusion of mathematics and physics into the subject. "Nature refuses to be unveiled by force. What she does not reveal to your mental sight you will not wrest from her with levers and screws." He refused to admit that yellow is red-green, that white is red-green-blue, and that black is a negative sensation.

He first advanced his theories in 1791 and would not be dissuaded by criticism from the completion of his monumental work, *Zur Farbenlehre*, in 1810—a two-volume

octavo of 1,510 pages and 16 colored plates. The observations recorded are astonishingly numerous and varied, from which artists have derived great benefit, as exemplified, to note only one instance, by their frequent discriminating use of colored shadows. Of this opus, Goethe wrote: "As for what I have done as a poet I take no pride whatever . . . but in my century I am the only person who knows the truth in the difficult science of colors—of that I say I am not a little proud." Two English translations have appeared, the first by Charles Locke Eastlake, the second by John Tyndall.

Though disdained by scientists, the monograph created a great sensation, and Goethe's views were widely accepted by philosophical writers, such as Hegel and Emerson. Herman Grimm declared, "Considered as a book . . . the *Theory of Colors* is truly enchanting." Lord Brougham, in his formal review, called the work a case of hallucination. The French Academy, at the advice of Cuvier, refused to consider it seriously. Helmholtz has labelled it as "the extravagancies of a great genius wandering out of his sphere."

Purkinje's dissertation on subjective visual phenomena, in 1819, won for him the friendship of Goethe, and partly through Goethe's influence Purkinje was appointed professor of physiology at the University of Breslau in 1823. Goethe's work inspired a psychologic school in which sensation rather than physical stimuli were stressed, with Purkinje, Brücke, Aubert, and Hering as typical representatives. The psychologic difficulties of accepting a purely physical interpretation of color have inspired several theorists to compromise hypotheses, such as those of Fick, Hering, and Ladd-Franklin.

On the night of his death, March 22, 1832, Goethe's last distinct words were "Mehr Licht! Noch mehr Licht!" and his keen eyes then closed forever.

James E. Lebensohn.

CORRESPONDENCE

Electrocoagulation of the Sclera

Editor,
American Journal of Ophthalmology:

I have read with interest the article in your June number by Dr. Harold G. Scheie and Dr. Bourne Jerome on this subject, and agree with the conclusion they draw that electrocoagulation causes shrinkage of the eye. This fact will be known to all surgeons who have operated on a detached retina and who have found that the cornea becomes hazy from raised intraocular pressure after several diathermy applications. This corneal haze caused by scleral shrinkage and raised pressure is relieved immediately if a scleral perforation is made.

The point of this letter, therefore, is to question the conclusions of your authors that shrinkage of the globe by this means might be employed as an alternative to scleral resection in the treatment of some detachments.

Electrocoagulation causes a severe intraocular reaction and for that reason can only be applied to the eye with safety in very limited amounts. To carry out this treatment over half the circumference of the globe and so produce sufficient shrinkage is an unwise procedure causing too much damage to the eye, and it is for this reason that scleral resection, which causes no severe intraocular reaction at all, is used in those severe detachments too extensive for diathermy to replace.

It will be known to those surgeons who have carried out scleral resection that the intraocular reaction is less than that of an ordinary diathermy operation.

I, therefore, give the opinion that while there is no doubt that electrocoagulation causes shrinkage of the sclera, this same method cannot replace surgical removal of a strip of sclera where this treatment is indicated.

(Signed) Seymour Philps,
London, England.

Dr. Scheie's reply

Editor,
American Journal of Ophthalmology:

The communiciation received from Mr. Philps serves to emphasize points brought out in our paper "Electrocoagulation of the sclera: Reduction in ocular volume and pathologic changes produced," American Journal of Ophthalmology, volume 32, part II, June, 1949, pages 60-78.

We demonstrated rather marked changes in the animal eyes used in our experiments with surface electrocoagulation. Engorgement of the retinal vessels, particularly in the nerve-fiber layers, associated with hemorrhagic phenomena was striking. The final retinal atrophy was considerable.

We concluded by stating, "although surface diathermy produced a high degree of scleral shrinkage, the associated pathologic changes were of such a severe nature that clinical application to this same extent would probably be inadvisable." Further work is now in progress on the problem.

(Signed) Harold G. Scheie,
Philadelphia, Pennsylvania.

Pterygium surgery

Editor,
American Journal of Ophthalmology:

In your issue of July, 1949, Dr. H. Saul Sugar paid me a graceful compliment by saying that it was the stimulus of my paper in the *British Journal of Ophthalmology* in February, 1948, that led to the writing of his paper on the "Surgical treatment of pterygium."

In return I would like to congratulate Dr. Sugar on his own well-conceived operation; I will pay him the practical compliment of performing his operation in Australia.

It would appear that Dr. Sugar is substantially in agreement with me, with the addition of certain very sound amplifications of his own, as to the essential nature of pterygium.

He feels, however, that my procedure of removing the whole of the subconjunctival tissue from the cornea to the plica semilunaris is fraught with danger to the internal rectus muscle.

Here I must beg to differ from my distinguished colleague for two reasons:

Firstly, as the subconjunctival tissue is dissected away from the uplifted conjunctival mucosa, held up vertically with fixation forceps by an assistant, interference with the underlying muscle cannot very well occur.

Secondly, over a period of some 10 years, no interference with the action of the internal rectus muscle has been noted, either by myself or by such of my Australian colleagues who use my technique.

In conclusion, however, this stimulating thought remains with me: how pleasant it is that an American surgeon, presenting his own excellent views on a subject, should give generous credit to a paper by an Australian, printed in a British journal.

(Signed) Arthur D'Ombrain,
Sydney, Australia.

First human electroretinogram

Editor,
American Journal of Ophthalmology:

As a footnote to the centennial perspective on "Electrophysiology," editorially noted by Dr. James E. Lebensohn in the August, 1949, issue of the Journal, it may interest your readers that an account of the first human electroretinogram was published by R. H. Kahn and myself (Arch. f. Ophth., 114:304, 1924). In Karpe's recent monograph on human electroretinography (1948), this priority is acknowledged. With grief I must add that my dear friend, R. H. Kahn, perished in Prague during the war.

(Signed) Arnold Loewenstein,
Glasgow, Scotland.

ELECTRICAL CONTROL FOR ASTIGMATIC CROSS

Editor,

American Journal of Ophthalmology:

In the September, 1949, issue of the JOURNAL, Dr. Horace L. Weston has an interesting account of an electrical method for revolving his astigmatic cross. Since I set up an arrangement similar to his four years ago, some suggestions may be of interest to others thinking of building such a remote control system.

One transmitter (control unit) may be made to drive an additional receiver—thus an astigmatic dial may be mounted in front of a pointer, the latter being rotated so as to indicate the most prominent line on the dial. As this receiver is driven in synchronization with the one turning the pointer, further setting of the pointer is minimized.

There is no need to use mechanisms which hum and require transformers for the surplus market is still glutted with fine units operating silently on 115-volts, 60-cycle A. C. These units are known as servo mechanisms. The two types are called transmitter and receiver. General Electric calls its units Selsyns (self synchronizing motors).

If the pointer and cross are not made extremely light, annoying chatter or oscillation will occur.

(Signed) Lee S. Sannella,
Petaluma, California.

BOOK REVIEWS

OCULAR SIGNS IN SLIT-LAMP MICROSCOPY. By James Hamilton Doggart. St. Louis, C. V. Mosby Company, 1949. 98 pages, cloth binding, 93 illustrations, 85 in color; bibliography, index. Price, $6.75.

In recent years there has been no small adequate textbook on slitlamp microscopy that has been available to the resident or student in ophthalmology. The text by Berliner is too ponderous and expensive. The monumental volumes written by Vogt are so difficult to obtain that they are not available for the student. The German language difficulty of the first two volumes is an additional handicap.

Thus Doggart's book fills a long-felt need, as a textbook for practical slitlamp microscopy for the postgraduate student.

As the author states in the preface, "bearing in mind the requirements of postgraduate students, the present writer has relegated the history of slitlamp microscopy to a short final chapter, and mathematical optics he has altogether eschewed. The apparatus is described in an appendix, and in order to forestall the criticism that this is the wrong approach, I would emphasize that such descriptions are seldom of interest, save to those who already know something about the apparatus. Therefore it is intended to plunge immediately into the clinical aspects of slitlamp microscopy with the object of helping the beginner."

The book is divided into nine chapters which discuss the value of the slitlamp technique of examination, the normal eye, corneal abnormality, aqueous disturbances, pathologic signs in the iris, lenticular changes, changes in the vitreous, and the evolution of slitlamp microscopy of the living eye.

On the whole the text is excellent. The chapter on the technique of examination is clear and concise and will be very helpful to the beginner in learning to use the instrument. The author's advice that slitlamp microscopy of the living eye should always be preceded by "naked-eye inspection" and by examination with the simpler methods is a factor that is all too often overlooked by the present-day student of ophthalmology. In discussing the pathologic changes a little more detail would seem to have been worthwhile.

In any textbook on slitlamp microscopy, colored illustrations are important. Of the 93 illustrations the book contains, 85 are in color. Some of the illustrations have been used in other books and publications of the author. Most of the pictures, however, are published in this volume for the first time. The original drawings are excellent and are

very well reproduced. They add a great deal to the value of the book.

The bibliography is comprehensive and is a good source of references for anyone interested in doing further work in some phase of slitlamp microscopy. Those books or journals giving further references to the literature are marked.

The index is complete and is an additional valuable factor in the book. The format and binding are excellent.

The book is a must for every student of ophthalmology.

Frederick C. Cordes.

REVISTA DE OFTALMOLOGIE. July-September, 1948, volume 1, pp. 1-204.

In this first volume of Rumania's new journal of ophthalmology, Bailliart publishes his reflections on the theories of vision, a subject for which he suggests a program of ophthalmic investigation. He also emphasizes the importance of a clear understanding of the specific photochemical and electrical reactions in the retina for other fields of science such as television which uses a mechanism similar to that of the retina.

Little is known of the details of the chemical composition or action of rhodopsin and its allied substances, of the functions of the rods and cones, the intercommunicating fibers of the different retinal layers, of the relative differences in the perceptive powers of the nasal and temporal retina, of the details of color vision, and of the shadow formation on the neuro-epithelium of the retinal vessels.

G. Bietti considers the etiology of trachoma and the effects of the sulfonamides and anitibiotics on this disease. The elementary and initial bodies cannot be considered to be Rickettsia because they are affected by the sulfonamides but are resistant to para-amino-benzoic acid which is specific for the Rickettsia. They cannot be interpreted as degenerated and phagocytized bacteria because they react to the sulfonamides and pencillin but not to streptomycin, in spite of the equal antibacterial effect of these substances. They are not degenerative reactions of the cells but are vital elements. All studies seem to suggest that the elementary and initial bodies are the corpuscular form of the trachoma virus.

A. Bussacca's article on pericorneal and corneal vascularization in keratitis is a chapter from his monograph on the pathology of the eye. He discusses the limbal network, superficial and deep vascularization, the exact localization and variation of corneal vessels and their involution. The paper is accompanied by several very good photographs and schematic figures.

In the longest paper of this volume, N. Blatt and M. Athanasiv report their study of the optic canal, a detailed and painstaking work in which they hoped to clarify the relation of the optic canal to diseases of the optic nerve. This paper contains a survey of the literature, a report on 10,000 adult and infant skulls, numerous tables, figures, X-ray pictures, and drawings. It discusses every possible variation in the appearance of the optic canal as found in 124 adults and 12 infants.

A. Franceschetti and C. Balavoine describe their method of keratoplasty. They use round corneal flaps, removed, if possible, within one hour after death and preserved in Ringer's solution on a specially constructed glass disc.

A. Kettesy proposes to standardize the examination of visual acuity. V. J. Munteanu describes three cases of dacryocystitis treated with pencillin. D. Lazarescu and P. Toporas discuss the physiologic variations of intraocular pressure. V. Sabadeanu and C. Henter contribute a paper on epidemic keratoconjunctivitis. N. Zolog stresses the allergic factor in phlyctenular keratoconjunctivitis and reports his experience with 25 patients treated with a hormone of the reticuloendothelial system which appears in large amounts in the blood of animals blocked by electronegative colloidal solutions.

Alice R. Deutsch.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

11
RETINA AND VITREOUS

Santoni, A. **Seasonal variations and frequency of retinal detachments.** Giorn. ital. oftal. 1:418-424, Sept.-Oct., 1948.

A statistical analysis of 610 cases of retinal detachment studied in the period from 1936 to 1947, showed a peak of incidence during the months of June and July, slightly less during May and August, and least in December. The possible significance of this finding is discussed.

Vito La Rocca.

Sautter, Hans. **Experimental spasm and the effect of vasodilators on retinal vessels.** Klin. Monatsbl. f. Augenh. **114**:333-346, 1949.

Visible contraction of retinal arteries can be brought about by intravenous injection of adrenaline. The dose necessary for this effect usually kills the animal. Injection into the vitreous leads at once to an ever increasing interruption of the retinal circulation. The vascular constriction is followed by a dilatation with secondary diapedesis of blood through the damaged capillary walls. The milky opacity during the constrictory phase is a pure ischemia. Intercellular edema is manifest during the phase of dilation as pseudocircinate retinitis caused by capillary damage. Hemorrhages and intercellular edema occur only during incomplete interruption of the flow of blood, never in complete embolism. Late effects of intravitreal injection of adrenaline into rabbits' eyes were degenerative changes in the choroid and pigmentary disturbances in the retinal periphery similar to retinitis pigmentosa. Vasodilators like acetylcholine and similarily acting agents were usually incapable of relieving the arterial spasm or the edema, even when injected into the vitreous. They were even less effective or seemed to increase the constriction if given in combination with atropine. The desirability of a new agent which dilates the vessels, but does not lower the blood pressure is stressed for the treatment of thrombosis and embolism. (8 figures, references.)

Max Hirschfelder.

Scheerer, R. **Retinal diseases from the viewpoint of the constitution theory of Kretschmer.** Klin. Monatsbl. f. Augenh. **114**:319-328, 1949.

The two basic types in Kretschmer's theory of constitution are the leptosome type and the pycnic type. The fundus of leptosomes usually shows thin arteries, a physiologic ischemia, a thin retina and a sclerotic choroid. The pycnic type shows a "moist" retina with broad vessels, and slight transparency and tends to approach the picture of a hypertonic fundus. Influence of general constitution is noted in several ocular diseases. Venous thrombosis is more frequent in the pycnic type with arteriosclerosis and other circular disturbances. Albuminuric retinopathy is more frequent in pycnic types, while chronic nephritis occurs in leptosomes. In glaucoma simplex one finds more leptosomes and in only 14 percent of them was vasoneurosis or arterial hypertension found. On the other hand, 67 percent of the patients with acute glaucoma, most of them of the pycnic type, had this finding. Life expectancy with acute glaucoma seems to be ten years less than with chronic simple glaucoma. Senile macular degeneration, found in "dry" retinas of chronic nephritis, occurs in leptosomes, whereas disciform degeneration of Kuhnt-Junius belongs to the "moist" retina of general vascular hypertension. (7 figures, references.)

Max Hirschfelder.

Scuderi, Giuseppe. **Macular retinitis of brown color.** Rassegna ital. d'ottal. **18**:82-96, March-April, 1949.

In 1946 Dejean and Laporte described a peculiar form of tuberculous retinitis of the macula and perimacular region. Its four stages are 1. a reddish-yellow alteration of the macular area of round or oval form, 2. the color changes to brick-red and the disc becomes hyperemic, 3. grayish nodules appear around the macula, 4. after several years black pigment spots are seen in a ring around, and in the macula. Scuderi's patient was a youth, 17 years of age, whose father had died of tuberculosis. Evidences of pulmonary changes were noted in the patient. The right eye only was affected. The article is illustrated with 8 figures, 4 in color, and 2 diagrams made by autoendoscopy by the patient.

Eugene M. Blake.

Stown, M. N. **Hyperplasia of the pigment epithelium of the retina simulating a neoplasm.** Tr. Am. Acad. Ophth. pp. 674-677, July-Aug., 1949.

The ocular condition in the left eye of a white man, aged 49 years, had been clinically diagnosed as von Hippel's disease ten years ago. Now sections showed marked proliferation of the pigment epithelium in a mass over the optic nerve head where bone changes also occurred. Some sections resembled neoplasm because of the marked proliferation of retinal epithelium. Lymphocytes, plasma cells and plasmacytoid cells diffusely infiltrated the anterior choroid. The retina was detached.

Chas. A. Bahn.

Verzella, Mario. **A new therapy for retinitis pigmentosa. Juxtabulbar injections of nicotinic acid.** Giorn. ital. oftal. **1**:331-358, July-Aug., 1948.

The author explains the characteristics of a new therapeutic technic based on intense hemo-dynamic action by massive local injections of nicotinic acid on the eye. After describing the technical modifications of injections, and trying to clarify the mechanism of action, the author reports concisely the history of 12 patients and the results obtained. He comments briefly on the favorable functional changes.

Vito La Rocca.

12

OPTIC NERVE AND CHIASM

Bedell, A. J. **Perineuritis optica.** Tr. Am. Ophth. Soc. **46**:399-411, 1948.

Four cases in which unusual signs

temporarily confused the diagnosis are reported and illustrated with serial fundus photographs. Serial fundus photography was also valuable in establishing the diagnosis in an unusual senile macular degeneration in a myope with hyperpiesia, a rare form of optic neuritis with a sharply localized edema of part of the nerve head in multiple sclerosis, syphilitic neuroretinitis simulating occlusion of the central retinal vein and traumatic retinal angiopathy, and tuberculous retinitis with severe optic nerve reaction and complete resolution of the focus with restoration of function. David O. Harrington.

Blatt, N. **The value of malarial therapy in syphilitic optic atrophy.** Ann. d'ocul. **182**:513-520, July, 1949.

The results of treatment in 387 cases of syphilitic optic atrophy during 20 years are analyzed. It can be easily seen that the prognosis of syphilitic optic atrophy is much worse in those treated with malarial therapy than in those treated by other methods or even untreated.

Chas A. Bahn.

Dresner, E., and Montgomery, D. A. D. **Primary optic atrophy in von Recklinghausen's disease (multiple neurofibromatosis).** Quart. J. Med. **18**:93-104, April, 1949.

The authors described three cases of optic atrophy in which multiple neurofibromatosis was the cause. Two of them occurred in uniovular twins. The third patient came to autopsy and an astrocytic glioma of the optic nerve was found. Primary optic atrophy has been found with von Recklinghausen's disease in 46 instances. In 41 cases in which histologic studies of the optic nerve were made there were 35 primary gliomas of the nerve or chiasm. R. Grunfeld.

Friemann, W. **Hereditary optic atrophy in women.** Arch. f. Ophth. **149**:266-274, 1949.

A pedigree is presented with familial optic atrophy in women of two generations. In Leber's optic atrophy men are usually affected. Ernst Schmerl.

Paufique, L., and Etienne, R. **Depressed colobomata of the papilla.** Ann. d'ocul. **182**:605-615, Aug., 1949.

This unusual developmental anomaly is usually unilateral and seldom multiple. The color of the depression is usually gray, involves ⅛ to ⅓ of the temporal part of the papilla, and its depth varies from 1 to 6 mm. Pulsation from the central retinal vessels may be observed. Vision is variably affected and central and paracentral scotomata may be present. In some cases a hereditary factor has been established, and other ocular degenerations such as macular cysts, congenital cataracts and microphthalmus may be coexistent. This anomaly is caused by an imperfect invagination of the primary optic cup. Two cases are described.

Chas. A. Bahn.

13
NEURO-OPHTHALMOLOGY

Capolongo, Giuseppe. **Chronaximetry in ophthalmology.** Riv. oto-neuro-oftal. **23**:371-386, Sept.-Dec., 1948.

The phosphene from an electric stimulus occurs at the level of the occipital cortex where the retina and the optic nerve are not intact and its chronaxy cannot be considered indicative of the functional state of the retina and the optic nerve. Melchiore Lombardo.

Cibis, P., and Lazar, O. **Disturbances of the lower visual functions in injuries of the brain.** Klin. Monatsbl. f. Augenh. **114**: 346-356, 1949.

In this statistical evaluation of 157 pa-

tients with brain injuries in World War II it was found that over one half of them had injuries to the posterior part of the skull. Of all the injured, 94 percent had better than half vision in the better eye and none was completely blind. Two of the patients had injuries of the optic tract with complete hemianopsia. The functioning half of the visual field reacted normally to adaptation tests, which is never found in injuries to the occipital lobe. About one third of the injured showed hemianopsias in the peripheral field, half of which were bilateral. A great majority showed "sparing of the macula" in the presence of peripheral hemianopic defects. The "spared area" showed damage of adaptation as well as of color distinction, which is ascribed to a change in the function of the cones in the area of central vision. (References.)

Max Hirschfelder.

Grignolo, Antonio. **A case of Claude Bernard-Horner syndrome from zona ophthalmica.** Riv. oto-neuro-oftal. **23**:387-392, Sept.-Dec., 1948.

A man, 57 years of age, soon after an attack of herpes zoster of the first branch of the trigeminus was found to have ptosis, miosis and enophthalmos on the same side. There was a spasm of the orbicularis, hypesthesia of the cornea and sluggish reaction of the pupil to light. The pupil became dilated after instillation of atropin and adrenalin but not of cocaine. This indicates that the lesion was between the superior cervical ganglion and the pupillary dilator just where the sympathetic fibers come in contact with the Gasserian ganglion. It is probable that the Horner syndrome was in this case caused by a diffusion by contiguity of the herpetic process from the trigeminus to the ocular sympathetic fibers.

Melchiore Lombardo.

Ohm, J. **The optokinetic tracts of the anterior corpora quadrigemina.** Arch. f. Ophth. **149**:248-265, 1949.

The author compares his own studies with those by Spiegel and Scala.

Ernst Schmerl.

Pampiglione, Giuseppe. **The electroencephalographic research in intracranial tumors.** Riv. oto-neuro-oftal. **23**:353-370, Sept.-Dec., 1948.

Many electroencephalograms are shown to demonstrate the importance of this test in the diagnosis and the localization of the cerebral neoplasms. (12 figures, references.)

Melchiore Lombardo.

Poos, F. **Paradoxical adrenaline mydriasis.** Ophthalmologica **118**:127-136, Aug., 1949.

The term paradoxical adrenaline mydriasis is applied to the well-known phenomenon of greater efficacy of topically applied adrenaline solutions in sympathetically denervated eyes. Instillation of adrenaline hydrochloride in 0.1-percent concentration produces appreciable mydriasis in the sympathetically denervated, but not in the normal eye. According to the conventional explanation of this phenomenon the denervated effector cells are more sensitive to adrenaline than the normally innervated dilator cells. The author is opposed to this concept of sensitization of the denervated muscle and adduces new evidence which suggests a different explanation. His main point is that the pupillomotor impulses elicited by changes in the light adaptation of the retina raise the threshold concentration of any mydriatic. The true threshold concentrations should be determined on sightless but otherwise normal eyes (a state apparently produced by severing the optic nerve close to the globe). A different and considerably higher threshold con-

centration is obtained if one determines the smallest concentration of a drug that overcomes the pupillomotor impulses serving retinal adaptation. Adrenaline in 0.1-percent concentration produces marked mydriasis in blind rabbits' eyes in which the retina no longer exerts its dominating effect upon the pupil. Even in normal rabbits' eyes a mydriatic effect of instillations of 0.1-percent adrenaline can be demonstrated if the observations are made at very low degrees of illumination.

The specific case of a marked change in the size of a sympathetically denervated pupil in man after the instillation of 0.1-percent adrenaline which produces no measurable change in the opposite, normal, eye may be explained as a result of the existing anisocoria. The width of the normal pupil is chiefly governed by retinal influences. A weak mydriatic would have to overcome these retinal influences in order to dilate the pupil. In the denervated, relatively miotic eye the weak mydriatic can produce a measurable dilation of the pupil without having to overcome the retinal pupillomotor factor and, moreover, the absorption of drugs from the conjunctival sac, the author believes, is better on the denervated than on the normal side. Peter C. Kronfeld.

Weekers, R., and Roussel, F. **The mode of action of retrobulbar injections of alcohol.** Ophthalmologica **118**:115-126, Aug. 1949.

The authors review the anatomy, physiology and pharmacology of the sympathetic and parasympathetic innervation of the anterior uvea. In order to elucidate the mode of action of retrobulbar alcohol injections in man, the authors have performed such injections in rabbits. The effects of these injections have been very uniform and consisted of mydriasis, diminution or abolition of the light reflex of the pupil, hypersensitivity to topical application of mecholyl and insensitivity to eserine. In most cases these effects have been transient and followed by complete recovery. The retrobulbar injection apparently produces a postganglionic, predominantly parasympathetic, reparable lesion. The sympathetic fibers escape injury because of their more dispersed course within the orbit. After retrobulbar alcohol injections in man, lasting pupillary disturbances are very rare. The authors report four such cases with pupillary reactions closely resembling those of Adie's syndrome. Some, but not all cases of Adie's syndrome are due to postganglionic parasympathetic lesions.

Peter C. Kronfeld.

14
EYEBALL, ORBIT, SINUSES

Heimburger, R. F., Oberhill, H. R., McGarry, H. I., and Bucy, P. C. **Intraorbital aneurysm; a case of aneurysm of the lacrimal artery.** Arch. Ophth. **42**:1-13, July, 1949.

A case of exophthalmos due to aneurysm of the lacrimal artery contained entirely within the orbit is reported. The lesion was removed by the transcranial route, and the patient is entirely well, over a year after operation, with normal vision and normal ocular movements. A survey of the literature revealed no other verified case of aneurysm of the lacrimal artery. Reports of six intraorbital aneurysms seen either at operation or at autopsy are reviewed, but in none is the diagnosis without question. The case presented is evidence that orbital aneurysm can be manifest clinically by unilateral exophthalmos without pulsation, but with evidence of venous obstruction, increased ocular tension and failing vision.

Ralph W. Danielson.

15

EYELIDS, LACRIMAL APPARATUS

D'Ermo, F. **Further contribution to the surgical treatment of the jaw winking phenomenon.** Boll. d'ocul. **28**:207-215, April, 1949.

After discussing previous approaches to this problem, D'Ermo describes two patients, aged 22 and 23 years, who were satisfactorily operated on according to the method of G. Bietti. His method is a combination of the technics advocated by Hess and by Angelucci. It was published by Bietti in the Boll. d'ocul. 21: 721, 1942. A large skin pocket is prepared by undermining the skin of the lid and separating it from the orbicularis muscle, beginning at the eyebrow and ending above the lid border. Separating the orbicularis fibers gives access to the levator muscle which is isolated and cut one half centimeter from its tarsal insertion. The distal muscle end is secured by three catgut sutures which are led through the frontalis muscle three centimeters above the eyebrow. Here, two more catgut sutures may be added on both sides of the original three sutures in order to strengthen the hold of the muscle stump in its new position. Two double-armed silk sutures are passed through the lid skin 4 millimeters from the lid border, from the outside towards the pocket, and led through the frontalis muscle to come to the surface 3 to 4 centimeters above the eyebrow. When the sutures are knotted, the two lower thirds of the cornea must remain uncovered by the upper lid. Regulation of the pull during the early postoperative period is indicated. The silk sutures are removed after 8 to 10 days. In both cases, the cosmetic result was satisfactory and the synkinetic movements with opening of the mouth, chewing, and lateral movement of the jaw were abolished. (12 figures, references.)

K. W. Ascher.

Nuti, F. **Etiologic explanation of a case of mycotic dacryocanaliculitis (Conistreptothrix Försteri).** Boll. d'ocul. **28**:169-178, March, 1949.

A 33-year-old woman developed purulent discharge from both canaliculi of her right eye one year after dacryocystectomy was performed. The opened canaliculi yielded numerous grayish-yellowish concrements some of which were inoculated into the anterior chamber of a rabbit, the remainder cultivated on aerobic and anaerobic media. In the rabbit eye the germ provoked a mild inflammatory process of the posterior corneal layers. The cultures proved the presence of a Conistreptothrix, most probably Försteri. Nuti raises the question whether some similar case previously attributed to actinomyces might have been caused by the same Conistreptothrix.

K. W. Ascher.

16

TUMORS

Negri, L., and Alajamo, A. **Tumors of the uveal tract and their cytogenesis.** Giorn. ital. oftal. **1**:289-316, July-Aug., 1948.

In a histologic study of 24 tumors of the choroid and one of the ciliary body stained with hematoxilin-eosin and a trichromic stain to show the reticulum, it was found that the pigmentation of the tumors is not enough for differential diagnosis on the basis of cellular morphology. They agree with Callender and Wilder that abundance in silver-staining fibers indicates less malignancy. The hypothesis of the origin of these tumors from a proliferation of the cells of the sheath of Schwann of the ciliary nerves deserves consideration, but requires further study.

Vito La Rocca.

Wolff, E. **The nature of the malignant choroidal melanomata.** Brit. J. Ophth. **33**: 445-452, July, 1949.

To support the theory that malignant choroidal melanoma is a sarcoma and that it is derived from the cells of Schwann of the ciliary nerves, Wolff points out that melanoma, like sarcoma, does not produce a local tissue reaction as does carcinoma. Blood vessels in sarcoma and melanoma are like new-formed vessels in that they have no walls of their own but are surrounded by tumor tissue. Teased tissue preparations show that the chromatophore and not the epithelioid cell is the essential cell of the melanoma. (6 figures.)

Morris Kaplan.

17
INJURIES

Ghose, Nirmal Kumar. **Unusual ocular foreign body.** Brit. J. Ophth. **33**:520-521, Aug., 1949.

The author describes an unusual irritating foreign body, a small snail that was removed after it emerged from under the conjunctiva. This organism easily survives in the sheltered subconjunctival tissue but rapidly dies upon exposure to air.

Orwyn H. Ellis.

Schreck, E. **Gas gangrene and the eye.** Klin. Monatsbl. f. Augenh. **114**:364-370, 1949.

The clinical, bacteriologic and histologic data on a patient who developed an intraocular infection with gas bacillus after perforation with a piece of metal are reported. Early panophthalmitis with rapid amaurosis and ocular hypertension and necrosis of the wound margins aid in the clinical diagnosis. Gas formation can sometimes be observed with the slit lamp or during operation. Gangrene of the ocular tissues with edema and necrosis as well as hemolysis and formation of methemoglobin were the pathologic characteristics. The patient received gas gangrene serum, sulfonamides and penicillin and recovered uneventfully after the enucleation of the bulbus. (3 figures, references.)

Max Hirschfelder.

18
SYSTEMIC DISEASE AND PARASITES

Ashton, N. **Vascular changes in diabetes with particular reference to the retinal vessels.** Brit. J. Ophth. **33**:407-420, July, 1949.

Histologic studies of vessel changes throughout the bodies of 21 diabetics were made and minutely compared. Tissues examined included those of the retina, choroid, ciliary body, iris, conjunctiva, brain, meninges, pleura, pericardium, omentum, peritoneum, bladder mucosa and the capsules of the kidney and liver. The details of fixing and staining all tissues are described. The suggestion that the lesions in the retina are micro-aneurysms is confirmed and it is shown that these dilatations occur in no other tissue. They occur mainly in the inner nuclear layer and are possibly caused at least partly by a venous stasis in this area brought about by fluctuations in ocular tension although this explanation is unsatisfactory and more work remains to be done. The retinopathy and the intercapillary glomerulosclerosis are very closely related etiologically and result from the same pathologic process whose manifestations differ in the eye and the kidney because of the different anatomic pattern of the retinal and glomerular vessels. (25 photographs.)

Morris Kaplan.

Botasso, Giovanni. **Posthemorrhagic amaurosis.** Rassegna ital. d'ottal. **18**:121-129, March-April, 1949.

Loss of sight from hemorrhage occurs most often from gastrointestinal and uterine hemorrhage, repeated blood-letting, epistaxis and hemoptysis, in the order mentioned. In only 12 to 15 percent of cases is the ocular involvement uni-

lateral and women are oftener affected than men. The author reports an instance of bilateral blindness occurring in a 45-year-old woman after a severe metrorrhagia. Eugene M. Blake.

Di Ferdinando, R. A. **A case of palpebral leishmaniasis.** Giorn. ital. oftal. **1**:359-364, July-Aug., 1948.

The author describes a case of palpebral leishmaniasis observed in a baby, 2 years of age, in the province of Pesaro-Urbino, where such disease occurs epidemically. He confirms the rarity of this dermatosis in comparison to its frequent appearance in other exposed parts of the body, which may be ascribed to local conditions of defense that hinder the action of the transmitting agent. Vito La Rocca.

Hartmann, Edward. **Psychosomatic phenomena in ophthalmology.** Brit. J. Ophth. **33**:461-476, Aug., 1949.

The author presents numerous case reports to illustrate psychosomatic problems in ophthalmology. Various responses such as esotropia in children and glaucoma in adults are produced. Functional disturbances are often associated with organic conditions and it is often important that the psychosomatic disturbance be alleviated before the organic condition will respond to treatment. (42 references.) Orwyn H. Ellis.

vom Hofe, K. **Participation of general factors in inflammations of the uvea and cornea.** Arch. f. Ophth. **149**:220-229, 1949.

Among the general diseases most often found in uveitis are rheumatism, tonsillitis, furunculosis, pneumonitis, otitis media and appendicitis.

Ernst Schmerl.

Ridley, A. **Toxoplasmosis, a summary of the disease with report of a case.** Brit. J. Ophth. **33**:397-407, July, 1949.

Prenatal infection of the eyes of human infants by the protozoon toxoplasma is being recognized and reported with increased frequency in all countries, and here the third case to be reported in England is presented. First discovered in 1908, the toxoplasma is an intracellular parasite whose presence is easily demonstrated in post-mortem material of most of the tissues and in vivo in the spinal fluid. In man, the severity of the disease and its predilection for the eye seem to vary inversely with the age of the patient. The eye manifestions include searching nystagmus, microphthalmos, persistent pupillary membrane, strabismus, lens opacities and, most seriously, focal choroiditis which is often in both macular areas. There is usually an associated focal encephalitis with multiple areas of calcification which are demonstrable on X-ray films. A diagnostic serologic test needs refinement. Treatment is disappointing although the combination of sulphonamides and emetine is recommended. (6 illustrations.) Morris Kaplan.

19

CONGENITAL DEFORMITIES, HEREDITY

Anderson, B. **Familial central and peripapillary choroidal sclerosis associated with familial pseudoxanthoma elasticum.** Tr. Am. Ophth. Soc. **46**:326-347, 1948.

A family pedigree is presented in which three of four siblings and one collateral relative have choroidal sclerosis and pseudoxanthoma elasticum. The sibling not exhibiting pseudoxanthoma elasticum presented angioid streaks and a retinal lesion resembling retinitis punctata albescens. The literature is reviewed. The hypothesis is advanced that the choroidal sclerosis is due to or associated with degeneration of the elastic membrane of the vessel wall. It is further postulated that the choroidal degeneration is due to localized anoxemia produced by the

changing pattern of the posterior ciliary arteries in the development of the orbital vascular and osseous system. The cases reported seem to substantiate the thesis that choroidal sclerosis is a clinical entity, a familial and probably a hereditary disease. Failure of the elastic tissue system may be the common denominator in angioid streaks, retinitis punctata albescens, choroidal sclerosis, pseudoxanthoma elasticum and retinitis pigmentosa.

David O. Harrington.

Azzolini, U. **The Laurence-Moon-Bardet-Biedl syndrome and similar clinical forms.** Riv. oto-neuro-oftal. **23**:309-340, Sept.-Dec., 1948.

The author differentiates a chronic arachno-diencephalic form of this syndrome which he ascribes to an inflammatory meningeal process in a tissue predisposed by heredity, whereas the usual manifestation is purely heredodegenerative. A clinical case is reported for illustration.

Melchiore Lombardo.

Burns, R. A. **Hereditary myopia in identical twins.** Brit. J. Ophth. **33**:491-494, Aug., 1949.

The detailed case studies and family pedigree of hereditary myopia in identical twins is reported. The twins were identical in all characteristics except for a difference in the refraction. The right eyes were almost alike but not the left. The family pedigree showed a dominant type of transmission which, however, did not appear in a later generation.

Orwyn H. Ellis.

Hepner, W. R., Krause, A. C., and Davis, M. E. **Retrolental fibroplasia and light.** Pediatrics **3**:824-828, June, 1949.

The effect of light as a causative factor of retrolental fibroplasia in premature infants was studied. The authors conclude that light is not a cause of this condition.

Donald T. Hughson.

Stadlin, W. **Chorioretinal changes in two sisters with Freidrichs' heredoataxia.** Ann. d'ocul. **182**:489-508, July, 1949.

This rare manifestation of this unusual disease is illustrated by two sisters whose parents were first cousins. The genealogy is traced through six generations of which they were in the fourth. The older sister was born in 1900 and the younger in 1903. Both were in good health until approximately the age of 15 years, when weakness developed in the lower extremities after an acute infection. Ataxia, scoliosis, loss of some reflexes, and ocular abnormalities slowly followed. Nystagmus was observed in both sisters about 1924. Now vision in the older sister is .1 in each eye and in the younger, .6 in each eye. The macular regions are irregularly pigmented and more so in the older. In the equatorial region the fundi contain 10 to 20 yellowish areas of various size and shape located in the external retina and choriocapillaris, most of which show moderate pigment migration. The discs and retinal vessels look normal, but the fields are moderately and concentrically contracted. The chorioretinal changes are slowly progressive. Their inflammatory or degenerative origin and the classification of tapeto-retinal degenerations alone or co-existent with cerebral and/or spino-cerebellar degenerations are discussed thoroughly.

Chas. A. Bahn.

Wilson, W. M. G. **Congenital blindness (pseudoglioma) occurring as a sex-linked developmental anomaly.** Canad., M. A. J. **60**:580-584, June, 1949.

The author constructed the pedigree of six generations of an Indian family in which several males were born blind. All the females except one were free from the disease. The transmission of the defect thus revealed sex-linked characteristics. Eyes that came to enucleation from three males showed the presence of gross de-

velopmental anomalies. The eyes of males that were seen in early infancy proved to have pseudoglioma due to excessive congenital detachment of the retina.

R. Grunfeld.

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HYGIENE, SOCIOLOGY, EDUCATION, AND HISTORY

Csapody, I. **Writing and the surgeon.** Szemészet **2**:85-91, 1949.

Surgical skill often manifests itself in handwriting. Three types can be distinguished: the ease in the writing of born artists' hands, the more expressive writing of energetic people, and the small letters of careful people. Security associated with ease is the common feature of suitable hands. Consciously nice writing is a good training for both skill and will. Analysis of writing may be employed in judging candidates. Gyula Lugossy.

NEWS ITEMS

Edited by Donald J. Lyle, M.D.
601 Union Trust Building, Cincinnati 2

News items should reach the editor by the 12th of the month but, to receive adequate publicity, notices of postgraduate courses, meetings, and so forth should be received by the editor at least three months before the date of occurrence.

Deaths

Dr. John Arthur Spengler, Geneva, New York, died August 12, 1949, aged 81 years.

Miscellaneous

Grady Clay Memorial Eye Clinic

On September 15th dedication ceremonies for the Grady Clay Memorial Eye Clinic were held at the Grady Clay Memorial Hospital, Atlanta, Georgia. The Grady Clay Memorial Eye Clinic is the result of the work of friends of the late Dr. Grady Edward Clay, professor of ophthalmology, who died July 12, 1946.

From the time of his appointment as head of the department of ophthalmology in 1939 until his death, Dr. Clay worked to develop an outstanding graduate training program in ophthalmology at Emory University.

Dr. Phinizy Calhoun, Sr., emeritus professor of ophthalmology at Emory University, delivered the dedication address and was followed by Dr. J. Mason Baird, director of the Grady Clay Memorial Clinic. The Grady Clay Memorial Eye Clinic building was accepted by Dr. R. Hugh Wood, dean of the Emory University School of Medicine and Dr. Alton V. Hallum, acting head of the department of ophthalmology.

The Grady Clay Memorial Eye Clinic is a two story, air-conditioned, brick building. It houses the out-patient clinics for the department of ophthalmology and the Montgomery Ophthalmological Laboratory, under the direction of Dr. Phinizy Calhoun, Jr. Instruction and conference rooms for graduate and undergraduate education and a library for ophthalmology, which is a part of the Emory University Medical Library, are also housed in the building.

Dr. Morgan B. Raiford, is fulltime clinical director of the clinic. Glaucoma and motility clinics have been organized.

Estelle Doheny Eye Lecture

The third Estelle Doheny Eye Lecture presented by the Estelle Doheny Eye Foundation will be given by Dr. Phillips Thygeson, at Los Angeles on January 17, 1950. Dr. Thygeson is associate professor of ophthalmology at the University of California Medical School in San Francisco. The subject of the address will be "The etiology and treatment of phlyctenular keratitis."

The lecture, an integral part of the foundation's functions, is named for Mrs. Edward Laurence Doheny, the foundation's benefactress. Dr. Alan C. Woods delivered the first annual lecture on December 17, 1947, and Dr. Cecil J. O'Brien, the second lecture on November 8, 1948.

Societies

Washington officers

New officers of the Washington, D.C., Ophthalmological Society are: President, Dr. J. Thomas Schnebly; vice-president, Dr. Thomas A. Egan; secretary-treasurer, Dr. Everett S. Caldemeyer; directors, Dr. Joseph Desoff and Dr. Jerome A. Sansoucy.

The meeting dates for the 1949-1950 season are November 7th, January 9th, March 6th, and May 1st. The March 6th meeting will be held jointly with the Baltimore Ophthalmological Society.

On November 7th, a dinner meeting was held at the Kennedy-Warren Hotel. Dr. Raynold N. Berke of Hackensack, New Jersey, spoke on "Ophthalmology in India," and films depicting the status of ophthalmology in India were shown.

Akron officers

Recently elected officers of the Akron Academy of Ophthalmology and Otolaryngology are: President, Dr. C. R. Anderson; vice-president, Dr. Daniel Mathias; secretary-treasurer, Dr. A. L. Peter.

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COLOR ILLUSTRATIONS—VOLUME 32, 1949

SUBJECT INDEX

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